Brain

A Journal of Neurology

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BRAIN.

PART 3, VOL. 61.

PICK'S DISEASE—A SPECIFIC TYPE OF DEMENTIA.

BY IRA C. NICHOLS AND WALTER C. WEIGNER.

(Butler Hospital, Providence, R.I.).

PICK (1892) first described certain progressive dementias showing lack of initiative, aphasias, and finally a vegetative existence terminating in a relatively early death from intercurrent infection. At first he thought of these cases as simple senile dementias, but subsequent observers, after careful histological examinations of autopsy specimens, concluded that the condition required a separate classification, and to it they gave the name "Pick's disease."

Although the subject has obtained considerable Continental attention, there has been a relative scarcity of reported cases in the English and American literature. The present writers believe that the disease is probably much more common than the paucity of reported cases seems to indicate, and hope that the résumé of the condition and the case to be reported herewith will serve to further emphasize this condition as a specific type of brain degeneration with symptoms which differentiate it from other types of dementia. No definite ætiology has been established for this condition. It is perhaps an heredo-degenerative disease. This view is considered the most probable by Grünthal (1930). He notes that the disease has previously been reported as occurring in sisters, and adds two cases of his own in brothers. Thorpe (1932) describes a case in a woman whose father's brain, at autopsy, had shown an unusual degree of atrophy, and considers that he might well have had Pick's disease, although the diagnosis of senile dementia had been made at the time of his death. Familial mental disease is frequently noted in the case reports. Horn and Stengel (1930), as well as Merritt and Springlova (1932), remark upon many similarities in the pathology of this disease to the changes seen in amaurotic family idiocy. Onari and Spatz (1926) call attention to the fact that there

are certain clinical and pathological features that link this condition to Huntington's chorea. Since these last two diseases are definitely known to be hereditary, these similarities suggest an heredo-degenerative ætiology for Pick's disease. Ferraro and Jervis (1936) have more recently made a special study of pathogenesis and decided that heredity could not be implicated. They consider that angiospasm plays an important though not exclusive role.

As to the age of onset, the reported cases have shown their initial symptoms between the extremes of 42 and 72 years, with the sixth decade containing the greater proportion. From the published material to date, it seems that the disease attacks females much more frequently than males, the ratio being approximately two to one. So far as can be determined from the available data, there is no special racial incidence.

Schneider (1929) has arbitrarily divided the clinical course into three stages, which are roughly of equal length. This is perhaps convenient, but we must keep in mind that the disease itself is an uninterrupted process. The onset is usually insidious, often being initiated by slight personality changes that are only appreciated in retrospect. Some of the symptoms of the early mental changes follow: indifference in performance of duties, carelessness in dress, disregard for the usual proprieties, nomadism, petty crime, apathy, failing memory, emotional lability, and motor unrest.

As the disease progresses we see in typical cases the development of characteristic symptoms. These are of the type which we associate with frontal lobe disease. The general character of these symptoms has been well described by Goldstein and Katz (1937). A. Stief (1930) noted a form of response suggesting echolalia, in which a prominent feature was minimum expenditure of ideational effort. In the case to be reported, this was a striking feature also. These individuals in replying to questions simply take the interrogative sentence as given to them, make minimal changes in word order and person, and answer the question in the examiner's own words. It is readily seen that this form of response is the most economical of thought. While well-accustomed acts may be long retained, all desire to vary behaviour spontaneously is lost. Thus as the disease progresses we find that the daily programme becomes stereotyped.

The subject of memory in these cases deserves special consideration. While, in the more familiar dementias, a failure of memory is usually an early prominent symptom, in a typical case of Pick's disease memory may be surprisingly intact in the early stages. While early observers reported a failing memory as an early symptom, subsequent studies revealed that it is not so much memory, itself, that is lost, but rather the use of it in the formation of new ideational material. This has been aptly described by

Kahn and Thompson (1934) as " the loss of memory as a tool." In our case, for example, while the patient superficially gave the appearance of deterioration, she was able to recall events with surprising accuracy when pressed for specific facts. Gordon (1935) brings out this point when, in describing his case, he states, " What is particularly striking is that in the midst of progressing dementia, his memory is to a very great extent preserved." The fact that memory is often long retained in this manner is perhaps one of the chief features which distinguishes Pick's disease from the other dementias.

When the second stage becomes more firmly established, hyperkinesias constitute a prominent symptom. This motor unrest is characterized by purposeless behaviour, such as slapping the thighs, tapping the floor, rocking back and forth, making clucking noises, and many other forms of diffuse stereotyped activity.

Another feature which may appear at this point is the occurrence of forms of aphasia. These may be of any type or combination of types, depending upon the associative area or areas involved. While every form has been reported, loss of speech is probably the most frequent. Horn and Stengel collected a group of cases in which apperceptive blindness was a prominent symptom. As the disease progresses, dementia becomes evident, but psychotic symptoms, such as hallucinations, delusions, confabulation and illusions, are rare.

In the third stage, cortical function is so diminished that the patient gradually sinks into a state of extreme hebetude, from which, finally, there is release by death from some intercurrent disease. While epileptiform seizures may occur late in the disease, they are rare. If they occur early, they speak against a diagnosis of Pick's disease. Throughout, physical signs are notably absent, although extra-pyramidal forms of rigidity may occur near the end. The total duration from the first symptom to the inevitable fatal outcome is generally between three and five years, with the reported extremes of two and twelve years. The case to be reported died nine years after the development of symptoms, which date of onset was well established by careful investigation.

In Pick's disease, laboratory examination of all the body fluids, including the spinal fluid, is negative.

X-ray examination of the skull, itself, may reveal thickening of the vault and that type of hyperostosis which sometimes follows atrophy of the underlying cerebrum. Upon encephalographic examination, the importance of which is stressed by Bumke (1929), we find generally enlarged ventricles, which may show dilatations corresponding to the atrophied portions of the brain. The subarachnoid air is seen lying in irregular masses

over the cortex, especially in the frontal regions, and filling the dilated insulæ and the cisterna chiasmatica.

There have been several reviews of the pathology of this condition during the past few years, the most complete being those of Onari and Spatz, of Horn and Stengel, and of Ferraro and Jervis. The findings revealed by necropsy may be outlined as follows: The skull is thick and may show hyperostosis. Plaques of leptomeningitis are frequently seen. The brain itself shows evidence of a more or less diffuse atrophy, with localized, roughly symmetrical areas of marked shrinking. Most typically, this process involves the frontal lobes, the first and second temporal convolutions, the insulæ, and the supra-marginal and angular gyri. The occipital and parietal lobes are occasionally involved. The pre- and post-central areas are usually strikingly spared. The brains frequently weigh much less than 1,000 grms. In Thorpe's case, for instance, the weight was 770 grms. In the reported cases, the left hemisphere has usually weighed less than the right.

Microscopic examination of the affected cortical areas reveals an intense loss of nerve cell elements, which reaches its highest degree in the three upper layers of the cortex. The cells are in part replaced by a strong glial reaction. Those which remain are either shrunken or present a bloated appearance. Although Alzheimer's argentophile inclusion bodies are numerous in Pick's disease, and although their presence in such numbers is one of the criteria upon which the pathological diagnosis is made, their real significance is still a subject of controversy. Williams (1935), for example, maintains that Pick's cells are not dependent on the senium or on specific ætiological agents for their development. von Braunmühl (1930), and Merritt and Springlova have described Pick's cells in cases of Lissauer's dementia paralytica. From these investigations it would appear that Pick's cells can and do occur apart from the entity called Pick's disease. Senile plaques and Alzheimer's fibrillary changes are typically absent, but, if present in moderate degree, do not exclude the diagnosis of Pick's disease. Changes in the blood-vessels are so insignificant that they cannot be considered as a factor, although Ferraro believes that angiospastic factors may play an important role. Inflammatory changes are absent. No evidence of acute softening is seen. Blood-vessel sprouts are lacking. von Braunmühl (1930) stresses the occurrence of degenerative changes in the extra-pyramidal nuclei. The general systemic examination shows nothing except those changes associated with the intercurrent disease which caused death.

The differential diagnosis is rather difficult and deserves some emphasis. The gradual and rather insiduous character of the mental changes that occur in Pick's disease may resemble certain forms of General Paralysis.

However, negative serological evidence excludes a diagnosis of neurosyphilis. Early in the disease, the exclusion of brain tumour, especially those involving the frontal lobes, may present difficulties. The aphasias, which occur in the second stage, suggest temporal tumour. However, since in Pick's disease there is no increase in intracranial pressure, and the triad of papillœdema, headache, and vomiting is absent, the exclusion of neoplasm should not offer a grave problem. X-ray plates of the skull in Pick's disease often reveal thickening of the vault, whereas, with tumours, thinning and erosions are often present. The encephalographic picture seen in Pick's disease, with the symmetrically dilated ventricles and the abundance of air over the cortex, is conclusive evidence that neoplasm is absent.

Perhaps the most difficult differentiation is between Pick's and Alzheimer's diseases. This cannot be made on any one set of symptoms, but depends more upon the general picture. Pick's disease is more apt to resemble General Paralysis, while Alzheimer's disease tends toward the picture of senile dementia. Confabulation is typically absent in Pick's disease. Memory loss occurs early in Alzheimer's disease, whereas, while it may seem to be impaired in Pick's disease, careful study will reveal that such is not the case, but that, as previously described, use of it as a tool is impaired. Kahn and Thompson consider encephalographic findings to be very helpful in this differentiation. They state that in Alzheimer's disease the subarachnoid air lies in broad, blunted sulci, whereas in Pick's disease it tends to lie in irregular masses. In distinguishing Pick's disease from other forms of dementia, cerebral arteriosclerosis is characterized by the frequent antecedent history of headache, dizziness, and apoplectic phenomena, together with the presence and character of the memory defect and the findings of systemic and retinal sclerosis. Simple senile dementia should not present any difficult problem because of its later age of onset and the character of the memory loss which differs from that in Pick's disease, as has been discussed previously. While in the early stages, the behaviour and emotional reactions might suggest functional mental disease, the organic implications soon become obvious.

Case Report.

Mary S., white, married, aged 56, was admitted to Butler Hospital on January 23, 1933, because of increasing restlessness and personality changes. Family history revealed eccentricity on the part of one maternal cousin, alcoholism in another and mental disease in still another. Birth history and early development were normal. The patient had been a good student, graduated from a business college, and worked as an efficient clerk for nine years prior to her marriage in 1906. In spite of the fact that no contraceptive measures were ever employed, the patient never became pregnant. Catamenia was established at thirteen years, but periods, while

regular, were excessive, lasting ten days and accompanied by severe headaches, invariably most marked in the left frontal region. The menopause was completed in 1927 without any disturbing mental or physical symptoms. Concomitant with the menopause, the headaches disappeared. There is no history of abuse of drugs or alcohol. In personality the patient had been lively, friendly, and pleasant, sociable and an active worker, holding several offices in women's clubs. Her mood had been stable and her judgment always considered good.

In retrospect, it seemed that the illness began insidiously in the spring of 1928, at which time the patient was 51 years of age. The first symptoms were irritability, moodiness and periods of mild confusion when hard pressed by her active and varied interests. In the autumn of that year, the patient sustained a small laceration of her scalp in an automobile accident. She was not rendered unconscious, however, nor did she express any physical complaints after the accident. An X-ray of the skull was not taken at that time. The mental changes previously described definitely antedate that accident. From 1928 to 1931 a gradual loss of interest developed, together with deterioration of judgment, and disregard for the ordinary social proprieties. For example, she sent notices of club meetings to outsiders, rather than to the members. At one of the meetings she greeted a long-absent member by saying: "How have you been since your husband's suicide?" In the discharge of her household duties she had become stereotyped, preparing the same meal day after day until changes were suggested by her husband. Her mood gradually became superficial and her reactions rather childish. During 1932 she showed marked change in the character of her thinking. She initiated very little conversation and began simply to repeat phrases which she heard in the conversations of others. Her mood became progressively more superficial and took on a jocular tone. Gradually there developed a diffuse type of restlessness, which constituted the main problem in her care at home.

Examination on admission revealed the patient to be in good general physical condition. Neurological examination was negative, except for hyperactive, but equal, tendon reflexes. Examinations of all body fluids, including spinal fluid, yielded results which were well within normal limits.

Mental examination revealed her to be alert, pleasant, and co-operative. She giggled freely and her emotional responses in general were superficial. On a few occasions, when things were not exactly to her liking, she rose in fleeting childish indignation. Restlessness was present and of a diffuse, purposeless type, consisting of pacing about the ward and her room, fumbling with newspapers, magazines, flowers and other articles. At times she was noisy, tapping her feet loudly, clapping her hands and slapping her thighs, at no time giving any reason for this behaviour. Her spontaneous speech consisted of superficial, isolated remarks concerning her husband, her home and her telephone number. When questioned, she invariably repeated the question, changing the pronouns from the second to the first person, to suit the occasion. For example, when asked, "How do you feel?" she replied: "How do I feel? I feel fine." In her conversation, patient showed a marked restriction of the ideational field. She was unable to give reasoned responses or to elaborate thought material, and, when pressed, made some superficial evasion. The following excerpts from her stream of talk will illustrate these points:—

Q.—Did you have a nice breakfast this morning?

A.—Yes, I had a nice breakfast this morning.

Q.—What kind of cereal did you have this morning?

A.—What kind of cereal did I have this morning? I had oatmeal.

PLATE XII

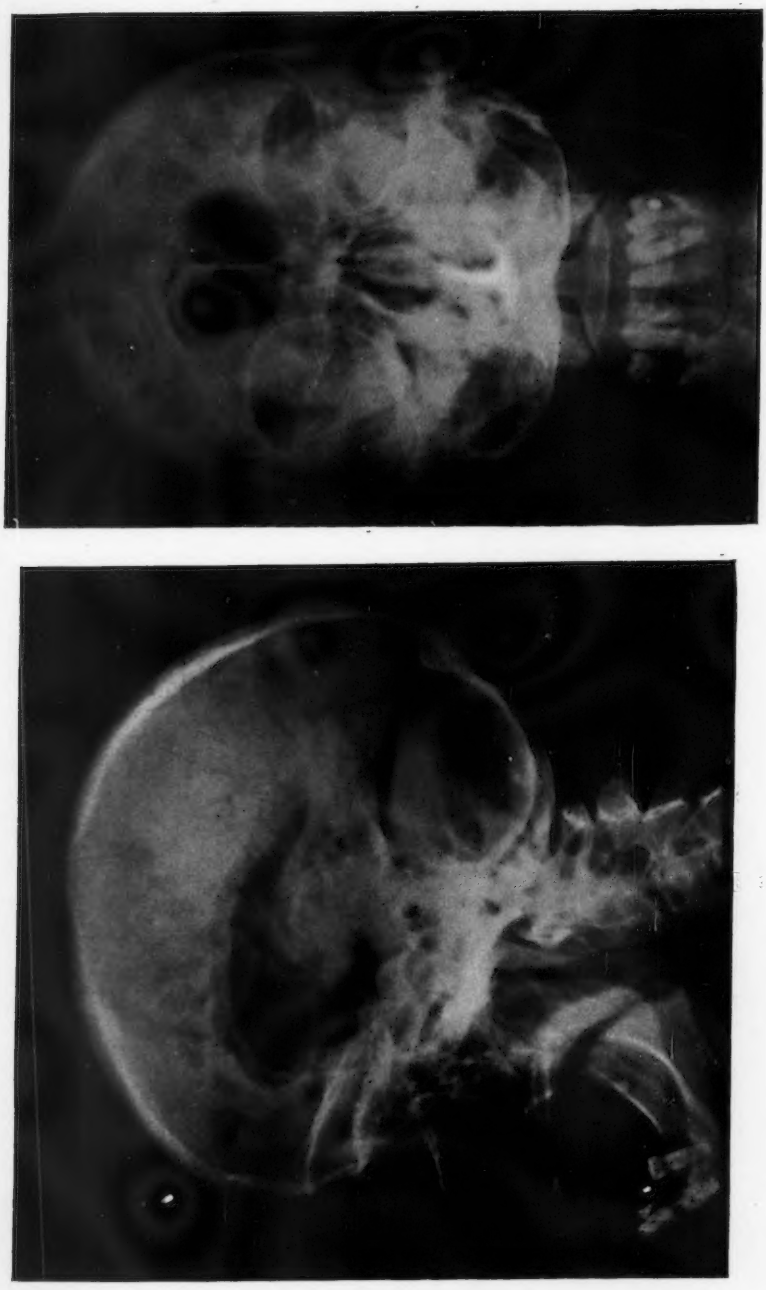

FIG. 1.

To illustrate paper by Ira C. Nichols and Walter C. Weigner.

PLATE XIII.

FIG. 4.

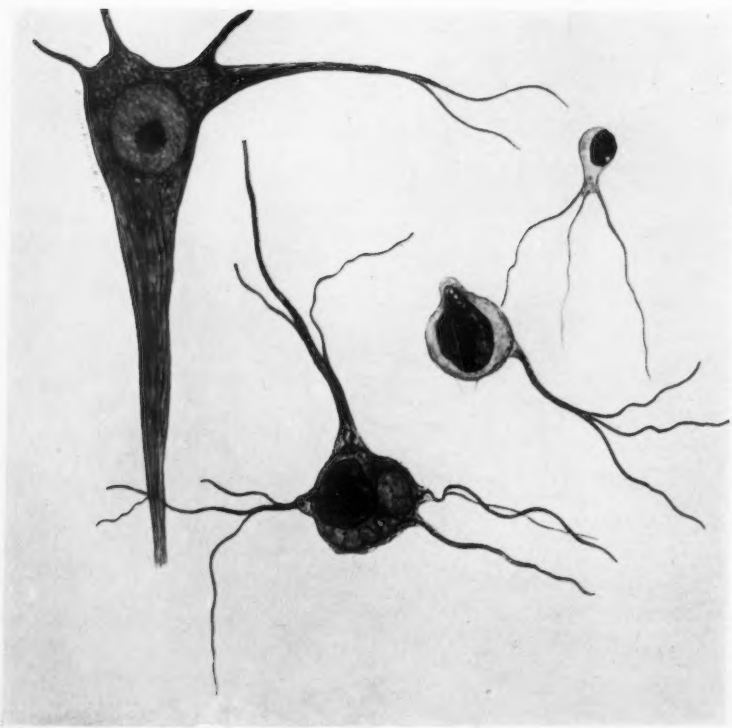

FIG. 5.

To illustrate paper by Ira C. Nichols and Walter C. Weigner.

Q.—Do you like oatmeal ?
A.—Do I like oatmeal ? Yes, I like oatmeal.
Q.—Why do you like oatmeal ?
A.—Why do I like oatmeal ? I don't like oatmeal. I like eggs.

She denied hallucinations and there was no evidence of their presence. No delusions were expressed. Memory showed no impairment in either the remote or recent fields ; in fact, memory seemed hyperacute. Her mental grasp was good ; she learned the names of doctors and nurses without difficulty, recognizing them on subsequent visits, and calling them by their proper names. Orientation was intact in all spheres. Insight was absent and judgment was extremely poor.

X-ray plates of the skull [1] revealed no evidence of old or recent fracture, or of increased intracranial pressure. The cranial vault was thickened and there were hyperostoses of the inner table in the frontal region. Encephalograms taken after the introduction of 100 c.cs. of air revealed symmetrical dilatation of both lateral ventricles, more marked in the anterior horns. The 3rd and 4th ventricles were normal. The cortical air pathways were not normally distributed and were dilated four or five times their normal width, indicating considerable cortical atrophy (fig. 1).

With a diagnosis of Pick's disease, the patient was discharged to her home on February 2, 1933. For the following six months she discharged her household duties satisfactorily, except for an increasingly stereotyped character to her daily programme. Gradually her defect of judgment became so marked that it was necessary for her husband practically to take over the management of the home. During the autumn and winter of 1933 and 1934 definite signs of a slowly progressing dementia showed themselves. Memory, which had previously been so acute, began to show minor lapses. Restlessness increased, mood showed further lightening and the ideational field showed gradual further restriction. It was in this stage of the illness that the patient was presented before the Boston Society for Psychiatry and Neurology (1934) Nichols, I. C., and Weigner, W. C., 1934.

Early in 1934 confusion was so great that the problem of wandering away from home necessitated re-admission to the hospital. At the time of this re-admission (February 10, 1934) no change was detected in her physical findings except that the hyperkinesia was more marked than formerly. Although she showed short episodes of confusion, her grasp of her immediate situation was still on the whole surprisingly good. During succeeding months increased untidiness developed to the degree that the patient was incontinent in bed and soiled her clothing. She showed absolutely no insight into this behaviour, simply giggling in a superficial manner when it was brought to her attention. Her previously described echolalic responses continued and, as time went on, it became increasingly more difficult to elicit any answers to questions put to her. Invariably she simply repeated the question in the same form that it had been presented to her. Occasionally she was noisy, chanting simple meaningless phrases at the top of her voice for long periods of time. By December, 1934, restlessness was definitely abating and intellectual faculties were undergoing obvious deterioration. Emotional responses were likewise undergoing change ; whereas formerly she was rather prevailingly euphoric, she was by this

[1] The authors wish to thank Dr. Isaac Gerber of Providence, Rhode Island, for his assistance in the roentgenological study of this case and for permission to use the plates.

time becoming flat in her emotional tone. In June, 1935, abnormal neurological signs were detected for the first time. She had a complete flexor withdrawal on stroking the soles of the feet, or on using the Oppenheim, Chaddock or Gordon manœuvres. Her general health was by this time failing, as indicated by a progressive loss in weight. By the end of 1936 the patient had deteriorated so greatly that she was practically mute. Occasionally she showed some excitement, which consisted in mischievous behaviour, characterized by meddling with other patients' possessions, tipping furniture over, rattling doorknobs, and the like. In the performance of this behaviour she showed great confusion and required almost constant nursing supervision. By the spring of 1937 she had lost a great deal of weight and

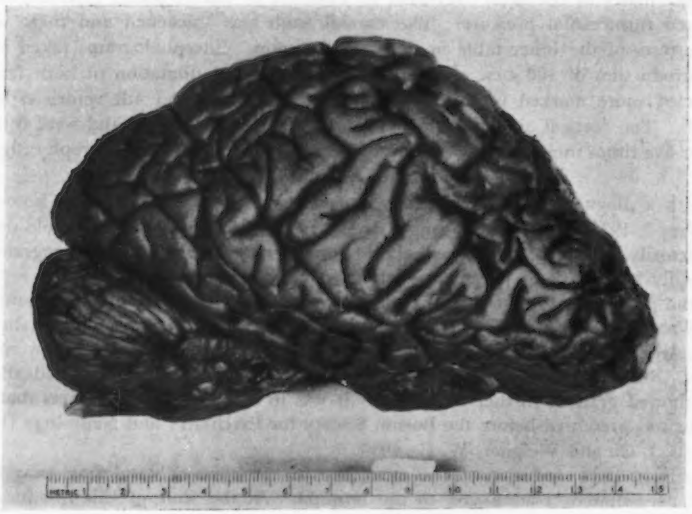

FIG. 2.—View of the right lateral surface. Note the shrunken gyri of the frontal regions which contrast so strikingly with the full-bodied appearance of the gyri in the region of the central sulcus.

was readily fatigued. On March 6, 1937, she developed a temperature and signs of pulmonary infection. On the evening of March 13, her temperature rose from 102·8° F. to 109·6° F., at which point she expired. A post-mortem examination was carried out four hours after death. The pathological diagnoses were: (1) Pick's disease (confirmation to be obtained in microscopic sections); (2) bronchial pneumonia, both bases, more marked on the right; (3) cholelithiasis; (4) congenital deformity of the left kidney—double ureter; (5) uterine fibromata; (6) localized arteriosclerosis: moderate in the arch of the aorta; marked in the abdominal aorta.

Gross and Microscopic Anatomy of the Brain.—The skull appeared thicker and denser than normal. The meninges exhibited no gross abnormality. In the circle of Willis there were only mild atheromatous changes. The brain weight was 950 grm. The brain appeared generally small, but the atrophy in the frontal and

temporal lobes was striking. The gyri in these regions were markedly shrunken and exhibiting a brownish discoloration. The sulcii of the atrophic regions were deep, wide, and gaping. On cutting the brain an increased resistance was met. On examining the cut surfaces the normal demarcation between cortex and sub-cortex could not be made out. The anterior horns of both lateral ventricles were dilated but otherwise the system was negative. The basal ganglia and the cerebellum showed no gross evidence of disease (figs. 2 and 3).

On microscopic examination the leptomeninges were normal. The pial and

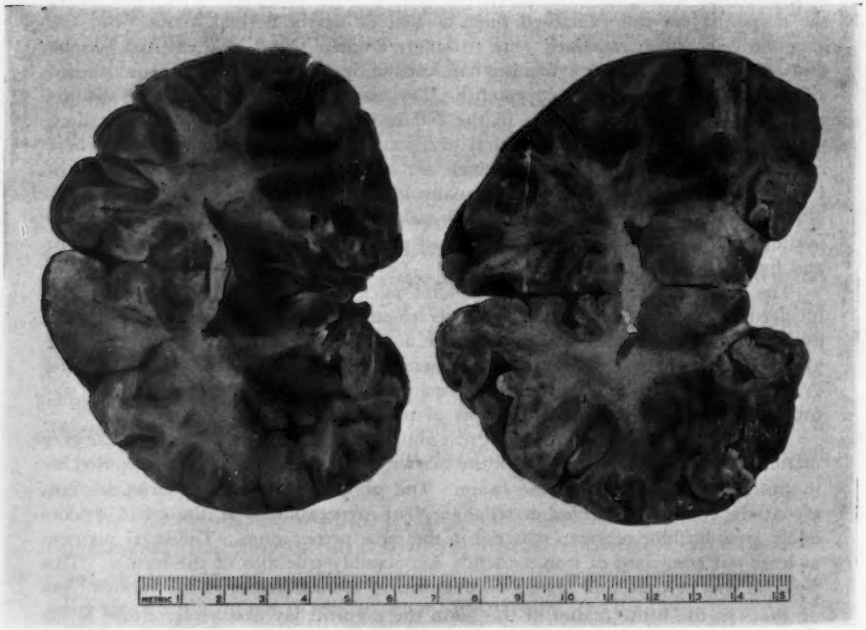

FIG. 3.—Coronal sections showing atrophy which is striking in the gyri of the basal portions of the hemispheres. The normal demarcation between white and gray matter is disturbed especially in the more atrophic gyri.

parenchymal vessels were remarkably free of atheromatous changes, except that the arterioles of the corpus striatum and the pallidal nuclei showed considerable calcification. There were, however, no foci of encephalomalacia resulting from these vascular lesions, nor any scars which could be attributed to them.

In the cerebral gyri, which had shown the greatest degree of atrophy macroscopically, the cyto-architecture was profoundly altered. Hardly a single ganglion cell remained in any of the cortical laminæ, yet the cellular population was increased in these layers above normal. The cells, however, were of the glial variety—astrocytes, oligodendroglia and Hortega cells being present in great profusion. There

was a conspicuous increase in the marginal glial cells and their processes which were coarse, tortuous and inserted in the membrana limitans (fig. 4). The glial cells and the fibroglial processes were somewhat more scant in the deeper layers where a status spongiosis was frequently in evidence. There was a condensation atrophy of the subcortical white matter in the frontal lobes. Here the oligodendroglial cells were exceedingly numerous and closely spaced, but no actual softening or progressive gliosis was present.

In the less atrophic gyri, such as the insular and cingulate, the microscopic picture was different. Here, only the superficial laminæ were depopulated of nerve cells; the deeper layers still contained their normal or nearly normal quota. But the ganglion cells which remained were strikingly altered. Most of them had become rounded and swollen, their cytoplasm had lost the tigroid markings and had assumed a homogeneous ground-glass appearance. The nuclei of these cells were less distinct and occupied eccentric positions in the cell bodies. In Bielschowsky preparations many of these cells lacked endoneural fibrils and relatively large numbers of them contained the argentophil spheres which are so typical of the histologic picture of Pick's disease. These spheres were usually larger than the nuclei which they displaced to the periphery of the cells. Occasional nerve cells in these less involved portions of the brain were not rounded and swollen at all, but were rather atrophic and hyperchromic (fig. 5).

The caudate nuclei, putamina, pallidal nuclei and substantia nigra were all involved in the atrophic process. In these structures the ganglion cells were slightly decreased in number and some were swollen or atrophic, but there was only moderate glial response. Only the caudate nuclei contained spongy zones. But these central gray structures were altered in another manner, and in this way compare with the cortex. There were enormous deposits of pigment.

Pigment granules were found in great abundance in the cortical and central gray matter and also in the subcortical white matter. In general, the greatest deposits lay in the atrophic portions of the brain. The pigment was of two varieties: one, a coarsely granular brownish material in Nissl preparations and, the other, a more finely granular blue or green material in the same preparations. The latter pigment at least was composed of iron, and this was possibly true also of the former. This pigment was in almost all instances contained in the cell bodies of the various types of glia. In the white matter of the brain the pigment lay exclusively either in the vascular sheaths or in scavenger cells in the perivascular spaces.

Sudan III preparations of the brain contributed much to the histopathological picture of this case. In them there was demonstrable a large amount of lipoidal material within the ganglion cells of the involved portions of the cerebrum. Sudan-staining particles were also found in abundance in the glial cells. Large scavenger cells filled with phagocytosed fat were found in the perivascular spaces of the frontal and temporal lobes, chiefly in the white matter. The large amount of this fat is surprising in view of the relatively negligible extent of the medullary sheath destruction as seen in Kultschitsky preparations. In these, the myelin of the centrum ovale, the corpora striata, the capsulæ extrema (externa and interna), and the pons, medulla and cerebellum were intact. The myelin of the cortex of the frontal and temporal lobes only was degenerated. Here, the cortical radiating fibres were fragmented and ballooned or entirely absent, and the subcortical fibres were poorly stained and appeared frayed or moth-eaten.

The cerebellum, pons, medulla, cervical spinal cord and occipital lobes were

unaltered. In the parietal lobes an occasional gyrus was involved. The frontal and temporal lobes suffered most of the injury, and the gyri of the orbital surfaces of the frontal lobes were injured most of all.[1]

Summary.

The dementias occurring during the latter years of life warrant study and clarification. This paper concerns itself with that specific type of dementia which was first described in terms of pathology by Arnold Pick. Although he first considered it as a form of simple senile dementia subsequent observers, adding to his findings, have concluded that it is a specific type of reaction with its own special symptomatology and pathology. Although the diagnosis in most of the reported cases was made post mortem, modern refinements in neuropsychiatric methods now make an earlier diagnosis possible.

Most valuable in our present day armamentarium is a careful psychological study of the memory. In cases of Pick's disease, this reveals a defect which often differs very characteristically from that found in the more usual dementias in that memory itself is not so much disturbed as much as the individual's ability to use it in the formation of new ideational material. It is this "loss of memory as a tool" that careful psychological study brings out. In addition to revealing this specific character to the memory defect, psychological examination also reveals frontal lobe symptoms such as psychical inertia, stereotypy, and disturbances of general and of ethical judgment.

The encephalogram is of great diagnostic value also. Inasmuch as the fundamental pathological process in the disease consists of circumscribed areas of atrophy—an enlargement of the ventricles and pools of subarachnoid air overlaying the atrophic areas are revealed by this method of study.

The course is progressive, leading to a relatively early death, which releases the individual from the vegetative existence of extreme dementia. The chief findings at autopsy are the strikingly circumscribed areas of atrophy which involve chiefly the frontal, temporal, and insular areas and less frequently the occipital and parietal lobes. The diagnostic criteria from the microscopic study are the severe diminution of cells, the intense gliosis, the presence of Pick's cells containing argentophil bodies, and the absence or paucity of senile plaques and Alzheimer's fibrillary degeneration.

A case is reported in which the diagnosis was made by means of the

[1] The authors wish to thank Dr. H. M. Zimmerman of the Laboratory of Pathology, Yale University School of Medicine, New Haven, Connecticut, for his invaluable assistance in the preparation and interpretation of the pathological material.

previously mentioned diagnostic procedures four years ante-mortem. The confirmatory post-mortem brain findings are described.

At the present time it is, of course, unfavourably regarded to call a disease by the name of its discoverer. It is particularly unfortunate in this instance for there is another Pick's disease, a polyserositis, and we also find that Niemann-Pick disease causes confusion. The term circumscribed senile atrophy, which is frequently used, is little better, for this does not separate this condition from other types of atrophy arising from other causes, and the term "senile" hardly suits a disease that may arise early in the forties. The ætiology is not indicated by the name, and since the causation is not definitely known, we believe we should frankly admit our ignorance and use the term idiopathic. In view of the facts to which reference has been made above, we suggest that a more suitable name would be "Idiopathic Circumscribed Presenile Cerebral Atrophy," which compensates for its clumsy length by a great increase in accuracy.

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LEGENDS FOR PLATES.

FIG. 1.—Lateral and anterior-posterior views after introduction of 100 c.c. of air. Note bilateral dilatation of the lateral ventricles extending well anteriorly. In the frontal regions air can be seen lying over the surface in broad irregular masses. In the anterior-posterior view collections of air in the insulæ are clearly shown.

FIG. 4.—Reconstruction of a Victoria blue preparation from the white matter of an atrophic gyrus showing the very rich proliferation of protoplasmic astrocytes. Many of these cells send processes to the walls of the blood-vessel.

FIG. 5.—Reconstruction of cells from a Bielschowsky preparation. Reading from right to left cells are represented in what is probably their progressive order of disintegration. The cell at the extreme right is relatively normal, while the one next to the left is bloated, its nucleus eccentric, and it contains a large argentophil body. The next two cells toward the left are shrunken, their nuclei are lost, and their chief features are the darkly stained argentophil bodies. (× 1,000.)

THE THALAMUS OF THE CHIMPANZEE.[1]

III.—Metathalamus, Normal Structure and Cortical Connections.

BY A. EARL WALKER, M.D.[2] AND J. F. FULTON, M.D.

The differentiated thalamic structures related to the visual and auditory systems in man and monkey have recently been studied intensively (Brouwer, 1936: Clark and Penman, 1934: Poliak, 1933), but the structure and connections of the anthropoid geniculate bodies have been described in only one case (Poliak and Hayashi, 1936). The close resemblance of the ganglia in the anthropoid to those of man, and the possibility of experimentation upon these animals gives particular significance to the study of their structure and relationships.

I.—Normal Structure.

Corpus geniculatum laterale.

The lateral geniculate body of the chimpanzee is similar to that of man and lower primates. It is an inverted, hemispherical, six-layered structure with narrow fibre bands separating the cellular laminæ. The intralaminar fibre zones between the inferior two layers are larger and more distinct than those between the other cellular laminæ. Through the anterior surface of the lateral geniculate body the fibres of the optic nerve enter these fibrous zones and ramify in the cellular layers. The six laminæ of the ganglion vary according to the site of the section. At its anterior and posterior extremities fewer cellular laminæ are present, and at both medial and lateral margins they coalesce forming only three or four distinct layers (fig. 1, Plate XIV).

Histologically, the lateral geniculate body may be divided into three parts, each with characteristic cytology: (i) the dorsal four layers, (ii) the basal two layers, (iii) the *grisea pregeniculata.* The dorsal four cellular laminæ are composed of uniform, medium-sized neurons fairly compactly

[1] From the Laboratory of Physiology, Yale University School of Medicine, New Haven, Connecticut. This work was aided by a grant from the Research Funds, Yale University School of Medicine.

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arranged. The cells are oval or circular in shape and clearly outlined, although a cell membrane can not be distinguished. The hyaloplasm stains diffusely in Nissl preparations. The dendrites are unstained although occasionally the axon hillock may be recognized. Numerous small and large chromatic granules are scattered throughout the cell. The pale-staining nucleus is well outlined by a distinct nuclear membrane. It is usually two-thirds the width of the cell. Numerous fine trabeculæ traverse the nucleus, many passing to the circular, diffusely staining nucleolus Satellitosis is uncommon, most of the neurons being devoid of glia or have only one glial cell. Scattered among the cells of this type are smaller, paler staining neurons comprising 10 to 15 per cent. of the total cellular mass.

The histological appearance of the neurons in the two basal layers of the lateral geniculate body is similar to that of the upper four laminæ, except that the cells are slightly larger, and less compactly arranged, the hyaloplasm more densely staining and the Nissl granules coarser.

Lying along the anterior surface of the dorsal portion of the lateral geniculate body is a loosely arranged collection of cells representing the *grisea pregeniculata.* The cells of this nuclear mass are slightly larger than those of the dorsal layers of the geniculate body, and polygonal or angular in shape. The hyaloplasm stains lightly so that the Nissl substance stands out clearly. The axon and dendrites of the neuron stain lightly giving a distinctly angular appearance to the cell. Satellitosis is the rule, two to four glial cells surrounding each neuron. The intensely staining nucleolus stands out prominently within the pale nucleus.

Corpus geniculatum mediale.

The medial geniculate body is an irregular mass of cells situated laterally between the inferior nucleus of the pulvinar and the lateral geniculate body, and the pes pedunculi medially. It is absolutely, but probably not relatively, increased in size, over its comparable structure in the macaque and lower primates. Its magnocellular division is smaller than that in the lower primates and its main portion is larger. At its rostral extremity large cells are widely dispersed so that the division between the two parts of the nucleus is difficult to distinguish. The relationships of the medial geniculate body are much the same as in the lower primates. Lateral to it is the nucleus pulvinaris inferior and the corpus geniculatum mediale, medially the nucleus peripeduncular and anterior tegmental nuclei and superiorly the nucleus suprageniculatus and ventral thalamic nucleus. With the exception of the nucleus suprageniculatus, which merges almost imperceptibly with the magnocellular portion of the medial geniculate body, the boundaries of the nucleus cause no confusion. The nucleus suprageniculatus is situated

anteromedially and is composed of dark staining, scattered cells, which are readily recognized in the normal specimen but may cause confusion in an area distorted by atrophy and gliosis (fig. 1, Plate XIV).

The main portion of the nucleus is composed of uniformly arranged, medium-sized, ovoid cells with large pale nuclei. The nucleus, occupying almost half the cell, is usually found at one end. The nucleolus is a prominent structure in the pale staining nucleus. Scattered irregularly through the lightly staining cell hyaloplasm are clumps of Nissl substance. Many neurons have one or two satellite glial cells. The magnocellular portion of the medial geniculate body consists of larger, more rounded but less compactly arranged, neurons. The hyaloplasm stains diffusely and more intensely; the Nissl substance is more prominent but regularly arranged in the cell. Although most of the neurons of the medial geniculate body are of these types, a few smaller, and paler staining cells are encountered.

Experimental Methods.

The animals used in this investigation were immature chimpanzees (*Pan satyrus*) which had been under observation for some time in the laboratory. General anæsthesia and complete surgical asepsis was used for all operative procedures. Both animals to be described lived more than six weeks after the final operative procedure. They were sacrificed under deep ether anæsthesia and the vascular system perfused immediately after death with saline followed by 95 per cent. alcohol. The thalami were quickly removed by blunt dissection in order to obtain optimal fixation. After hardening in 95 per cent. alcohol, the hemispheres were photographed, the lesions examined and minutely described. The lesions accompanied by a generous amount of surrounding cortex, were then further fixed in 95 per cent. alcohol and ether, and embedded in celloidin. Coronal serial sections were made of both the cortex and thalami. Every 25th section of the cortex was cut at 25 microns and stained by Nissl's thionin method. In one animal every third (Snookums) and in the other every fifth (Ghandi) section of the thalamus was stained by the same technique and mounted. All illustrations were made from direct projection of the sections. The lesions and degenerations (solid black or heavy stippling in the illustrations) were filled from direct microscopic examination of the sections. The number under each drawing indicates the section from which the drawing was made.

The following abbreviations have been used in the illustrations:—

CF.	fissura calcarina.
IH.	cornua inferiore, ventriculi cerebri.
IS.	sulcus intraparietalis.
L.	lateral.
M.	medial.
OD.	sulcus occipitalis diagonalis.
PE.	sulcus parieto-occipitalis externa.
PI.	sulcus parieto-occipitalis interna.
SS.	sulcus sylvii.
ST.	sulcus temporalis superior (parallel sulcus).

II.—Experimental Results.

In a previous study (Walker, in press), it has been found that in the chimpanzee after hemidecortication, the lateral geniculate body is virtually devoid of normal cells. Occasional cell shadows and shrunken cells were present especially in the lower two layers. The medial geniculate body, including its magnocellular portion, was found completely degenerated except for an occasional normal appearing cell. Its adjacent supragenicular nucleus was entirely spared, as were also the cells along the lateral portion of the cerebral peduncles and the *grisea pregeniculata.* It may, therefore, be assumed that practically the entire medial and lateral geniculate bodies project to the cerebral cortex. Details of this projection have been determined in the following two experiments.

Experiment 1.—Lesion of right occipital pole; degeneration of medial portion of the lateral geniculate body. Ablation of left occipital lobe and small lesion of the superior temporal convolution; severe degeneration of the left lateral and medial geniculate bodies. Weight 11·3 kg. (Snookums).

The subject of this experiment was a timid, temperamental young female chimpanzee, in excellent condition except for a desquamating dermatitis over the head and neck. On February 19, 1936, a right osteoplastic craniotomy was performed. The inferior half of the post-central convolution and the occipital operculum juxtaposed to the external parieto-occipital fissure were ablated. On April 2, 1936, a left osteoplastic craniotomy was performed exposing the occipital and posterior temporal regions. The left occipital lobe posterior to the parieto-occipital fissure was removed in one piece. The Sylvian fissure was opened and with a brain spatula the cortex lying on a small ridge on the superior surface of the first temporal gyrus was removed by subpial dissection. The neurological disturbances resulting from these ablations will be described in another connection. The visual disturbances were similar to those described by Spence and Fulton (1936). On May 28, 1936, the animal was sacrificed.

Anatomical Examination.

Right cerebral hemisphere.—The sites of two cortical lesions are as follows: One occupies the inferior two-thirds of the post-central convolution, and the second the rostral portion of the lateral surface of the occipital lobe, extending parallel with the parieto-occipital sulcus. It begins 1 cm. from the mid-line as a lesion 0·6 to 0·7 cm. in width tapering inferiorly to its termination just above the tip of the sulcus occipitalis diagonalis.

Serial sections of the occipital lobe confirm the gross location of the lesion. Its posterior margin borders upon striate cortex. The anterior margin on the posterior wall of the external parieto-occipital sulcus is bounded mainly by cortex of type 18 and in a few places by type 19. In the lower part of the lesion there is slight involvement of the annectant cortex of the posterior parietal lobe but the greater part of the apparent damage is the result of accidental hæmorrhage at the time of sacrifice, considerable fresh blood being present in the parieto-occipital sulcus and a small amount in the tissues of the cortex anterior to the external parieto-occipital sulcus.

There is, however, a small old superficial lesion of the anterior lip of this sulcus. In no place does the main lesion extend into the cortex for more than 1 to 2 mm. (fig. 2).

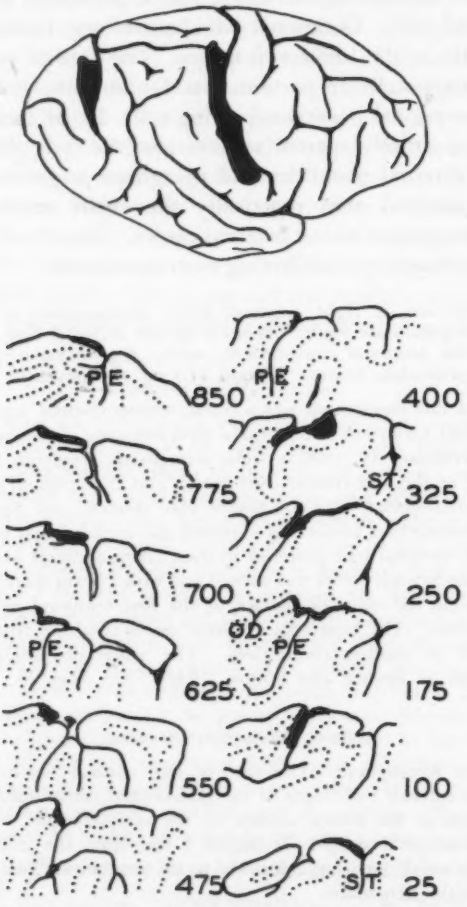

FIG. 2.—The right cerebral hemisphere of chimpanzee Snookums and sketches of serial sections of the occipital opercular lesion.

Right lateral geniculate body.—An examination of serial sections of the thalamus reveals a zone of retrograde cell degeneration along the medial aspect in the posterior half of the lateral geniculate body. The degeneration, involving all six layers, first appears along the extreme medial margin of the nucleus a few sections from the caudal pole. Anteriorly, it enlarges but maintains its medial and peripheral position through the posterior quarter of the nucleus. At this level a narrow zone of normal

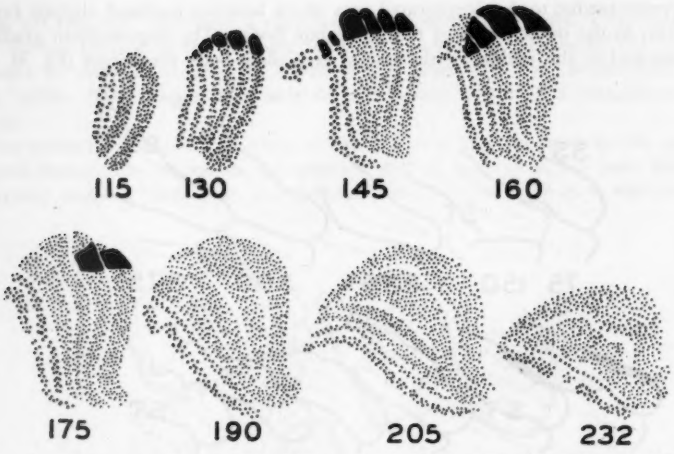

FIG. 3.—Representative serial sections of the right lateral geniculate body of chimpanzee Snookums showing the extent of the retrograde cell degeneration.

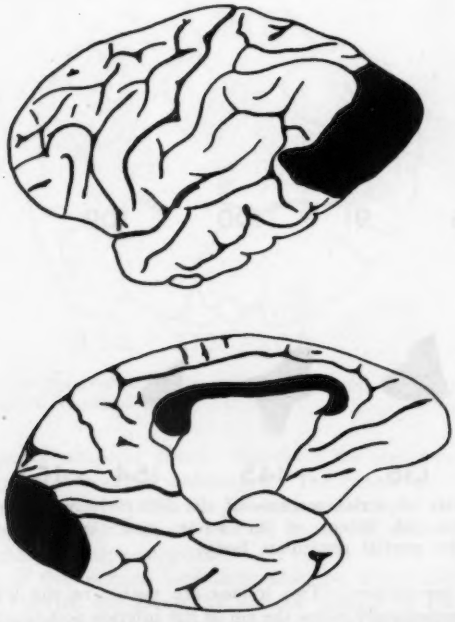

FIG. 4.—The left cerebral hemisphere of chimpanzee Snookums to show the site and extent of the cortical lesions.

cells appears medial to the degenerated area which becomes confined, slightly further anteriorly, to the outer layers of the geniculate body. The degeneration gradually decreases and at the middle of the lateral geniculate body disappears (fig. 3).

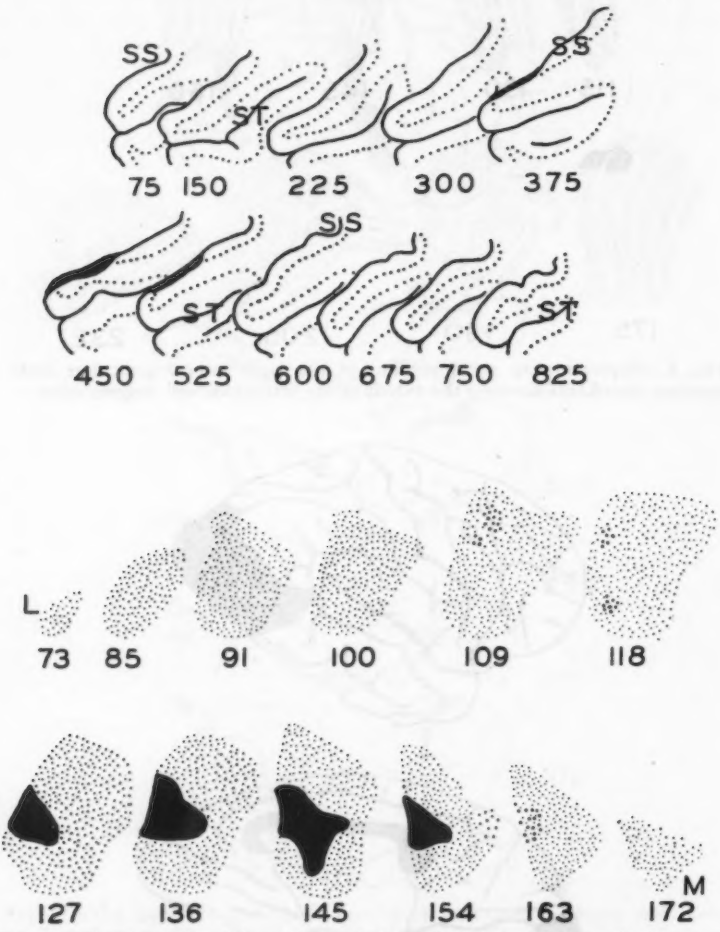

FIG. 5.—Sketches of serial sections of the left Sylvian region of chimpanzee Snookums to show the extent of the lesion, and (below) the retrograde cell degeneration in the medial geniculate body.

Left cerebral hemisphere.—Two lesions are visible in the left cerebral hemisphere (fig. 4). Immediately below the tip of the inferior post-central sulcus a linear injury 0·8 cm. in length lies along the superior margin of the first temporal convolution, but does not involve the cortex on the convexity of the gyrus. Serial sections

of the left temporal lobe show a superficial lesion entirely confined to the concealed intra-Sylvian portion of the superior temporal convolution. Laterally the lesion is bounded by Area 22 cortex, but medially and posteriorly by "koniocortex" (*see* Beck, 1938). The margin anteriorly is in temporal cortex of a transitional type (fig. 5).

The second lesion is an ablation of the occipital lobe posterior to the parieto-occipital fissure. The cortex on the anterior wall of this sulcus has been damaged in varying degrees. Inferiorly a superficial lesion extends almost to the posterior

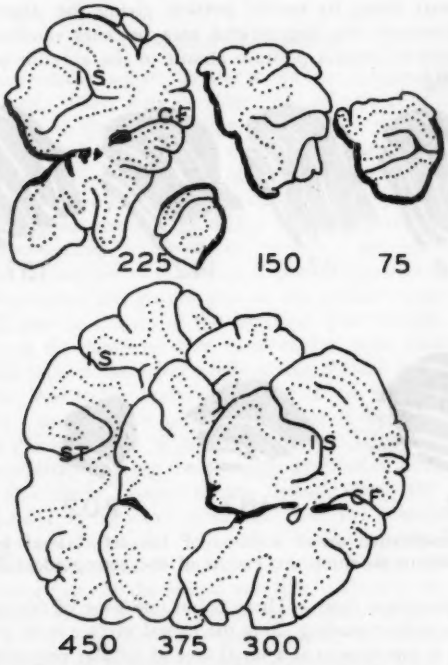

FIG. 6.—Serial sections of the left occipital lobe of chimpanzee Snookums to show the extent of the cortical lesion.

margin of the superior temporal sulcus. Superiorly the annectant gyri are injured but the superior parietal lobule is undamaged. The cuneus on the medial surface of the hemisphere is intact except for the ablated superior lip of the calcarine fissure. On the inferior surface of the occipital lobe the damage is more extensive than that on the medial surface of the hemisphere.

Serial sections of the occipital lobe show that the striate cortex of the lateral surface has been ablated, but along the anterior margin of the calcarine fissure within its depths a small strip is preserved on both lips. Somewhat more striate cortex is present on the superior than on the inferior lip of the calcarine fissure. Area 18 bounds the lesion about the depth of the parieto-occipital fissure, but the greater

part is bounded by cortex of Area 19. The lesion on the lateral surface of the hemisphere has this type of cortex on its margins except in the angular gyrus where Area 22 and Area 7 bound it (fig. 6).

Lateral geniculate body left.—Serial sections show that the left lateral geniculate body is severely changed. Its entire posterior pole is completely degenerated, but at about the posterior quarter of the nucleus a narrow zone of normal cells in all six layers appears on its inferolateral margin. The entire posterior half of the dorsal and medial portions of the geniculate body is completely degenerated. At approximately the middle of the lateral geniculate body a zone of normal cells appears along its medial portion giving the degenerated portion a wedge shape. Anteriorly the degenerated area becomes smaller and smaller but constantly maintains its central position almost to the anterior pole of the medial geniculate body (fig. 7).

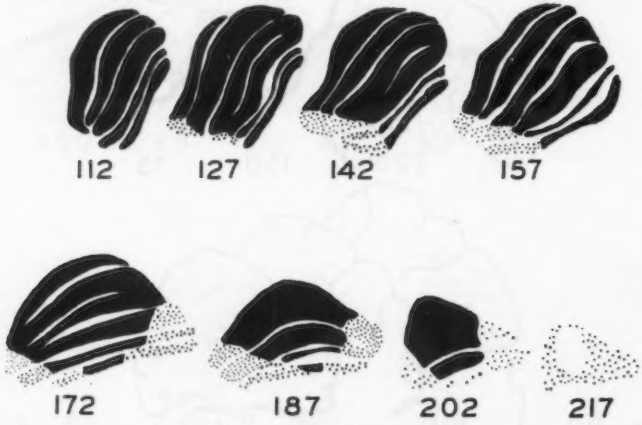

FIG. 7.—Representative serial sections of the left lateral geniculate body of chimpanzee Snookums to show the extent of the retrograde cell degeneration.

Left medial geniculate body.—There is but one zone of degeneration in the left medial geniculate body extending along the lateral surface in its anterior half. Near the posterior pole it commences as a small area of cellular degeneration in the dorsolateral portion of the medial geniculate body. This enlarges and coalesces with a smaller area which becomes apparent slightly more inferiorly, forming a well-defined area of complete cellular degeneration along the lateral margin. It is situated in the mid portion of the nucleus, ventrodorsal. Anteriorly the degeneration maintains its topographical position with slight changes in shape to near the rostral pole of the medial geniculate body. At this level the degeneration becomes scattered and disappears (fig. 5).

Experiment 2.—Linear incision in left superior striate cortex; degeneration in medial portion of the left lateral geniculate body. Ablation of first and second temporal convolutions on right severe degeneration of medial and lateral geniculate bodies. Weight 22·1 kg. (Ghandi).

The subject of this experiment was an immature but well-adjusted male chimpanzee. At the first operation, November 8, 1935, lesions were made in the

left motor leg area and superficially in the left supramarginal gyrus. On December 4, 1935, under sodium amytal anæsthesia a low right temporal craniotomy was performed with the assistance of Dr. E. H. Botterell. The first and second temporal convolutions from the tip of the temporal lobe to the inferior margin of the angular and supramarginal gyri were removed *en bloc*. Convalescence was uneventful. A third operation was performed on January 13, 1936, when the left premotor leg area was removed and linear incisions made in the post-central convolution. On February 18, 1936, under ether anæsthesia a small linear incision was made through a burr hole in the medial surface of the left occipital lobe. The animal was sacrificed April 3, 1936.

Anatomical examination.

All lesions were sectioned serially so that the precise extent of the injuries could be accurately ascertained. There were no subcortical softenings in the left hemisphere, and, since the lesion of the supramarginal gyrus was quite superficial, it seems fair to assume that it did not interrupt the visual radiation.

Right cerebral hemisphere is the site of a lesion occupying the first and second temporal convolutions extending from the tip of the temporal lobe posteriorly for 3 cm. and inferiorly from the Sylvian fissure and the cortex of the island of Reil both of which appear undamaged. Posteriorly a part of the superior temporal convolution remains and the margin of the lesion slopes inferiorly to the middle temporal sulcus. This sulcus forms the greater part of the inferior margin of the ablation. Anteriorly a small part of the tip of the temporal lobe remains.

Serial sections of the temporal lobe confirm the gross location of the lesion. Its superior margin follows the lower angle of the Sylvian fissure from almost the tip of the temporal lobe to the posterior margin of the insula sparing entirely the cortex of the latter. At this point on the inferior lip of the Sylvian sulcus, cortex of the granular type ("koniocortex") bounds the lesion. The latter rapidly becomes superficial, thus completely sparing the posterior and medial portions of the auditory "koniocortex." The lower border of the lesion along the inferior temporal convolution is bounded by cortex of Area 20. Near the posterior extremity of the lesion cortex of Area 21 appears. The lesion extends deeply into the substance of the temporal lobe but a narrow margin of white matter surrounds the lateral surface of the inferior horn of the lateral ventricle. There is no evidence of direct damage to the striate cortex in any part of the lesion. In fact there is no striate cortex in any section of the cortex cut well posterior to the lesion. The anterior two-thirds of the first and second temporal convolutions have thus been largely ablation, i.e. Areas 22, 21, and auditory "koniocortex" (fig. 8).

Right lateral geniculate body.—Serial sections reveal marked degeneration in the lateral part of the anterior half of the lateral geniculate body. At approximately the rostral extremity of its posterior quarter scattered degeneration is present at its lateral margin. Anteriorly this area increases in extent. In the degenerated areas, however, a few normal cells always remain, a condition which is quite unlike the degeneration produced by damage of the striate cortex itself. In the anterior half of the lateral geniculate body, the changes become more intense and its margin is completely degenerated. An intermediate zone between the completely degenerated and the normal exists in which only scattered degeneration is present. The medial half is normal throughout (fig. 9).

Right medial geniculate body.—Serial sections of the medial geniculate body

show marked degeneration with severe gliosis in its entire inferior portion. A zone of degeneration in the inferior fourth of the medial geniculate body extends from the posterior pole to the middle of the nucleus. At this level a narrow layer of

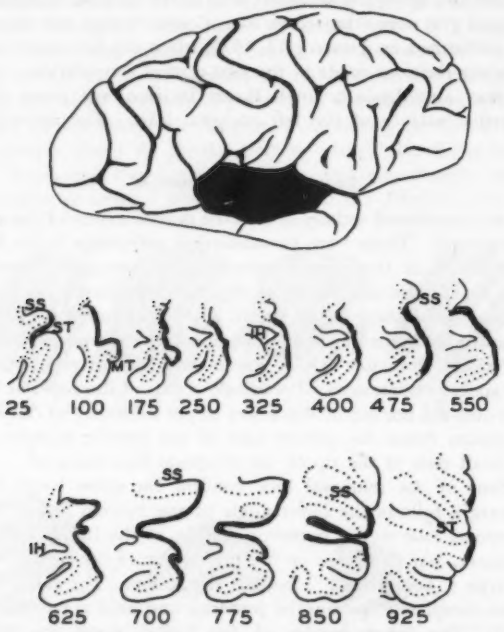

FIG. 8.—The right cerebral hemisphere of chimpanzee Ghandi showing the extent of the temporal ablation and serial sections of the lesion to show its precise limits.

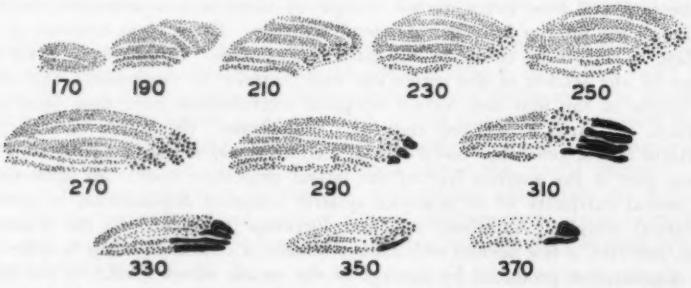

FIG. 9.—Representative sections of the right lateral geniculate body of chimpanzee Ghandi to show the extent of the retrograde cell degeneration.

normal cells appears along the inferior margin of the medial geniculate body. Further anteriorly this layer increases in thickness so that the degenerated zone extends as a transverse band across the medial geniculate body. At the oral

ERRATUM.

On Plate XIV, facing page 260, Part 3, 1938 (Article: "The Thalamus of the Chimpanzee," Walker and Fulton.) Fig. 1. The upper illustration should be the lower, and both should be inverted.

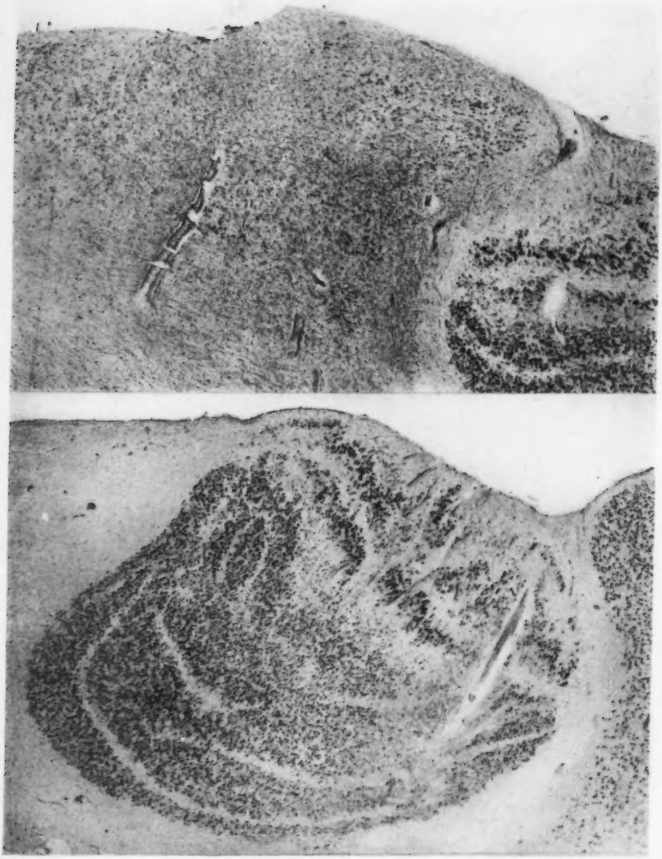

FIG. 1.—The structure of the lateral (above) and medial (below) geniculate bodies. In the lateral geniculate body (chimpanzee Ghandi, left section 260) is an area of retrograde cell degeneration involving the outer four layers. A horizontal layer of cellular degeneration is present in the medial geniculate body (chimpanzee Ghandi, right section 255).

FIG. 10.—Photomicrograph of the right geniculate body of chimpanzee Ghandi (section 300) to show the type of cellular degeneration (compare with fig. 1).

To illustrate article by A. Earl Walker and J. F. Fulton

extremity of the nucleus the changes are less intense and normal cells are interspersed in the degenerated area (fig. 11).

Left cerebral hemisphere.— A linear incision lies just posterior to the external parieto-occipital sulcus parallel to the longitudinal fissure. It measures 0·6 cm. in length and is 0·3 cm. from the mid-line. Serial sections of this block from the medial

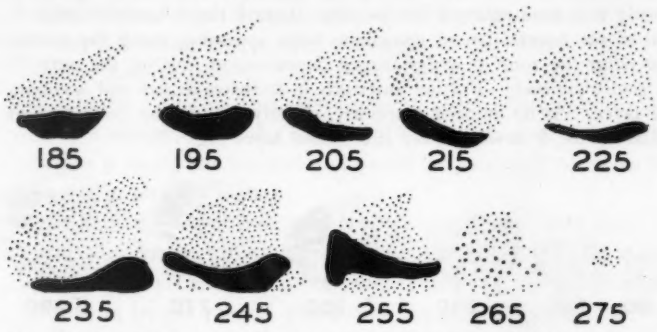

FIG. 11.—Serial sections of the right medial geniculate body of chimpanzee Ghandi to show the extent of the retrograde cell degeneration.

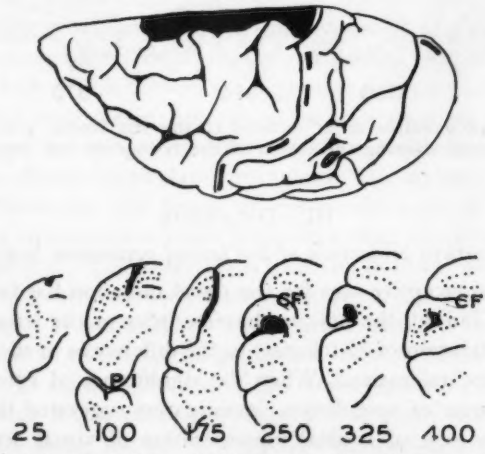

FIG. 12.—The left hemisphere of chimpanzee Ghandi showing the site of the cortical lesions, and (below) representative serial sections of the occipital lobe lesion to show its precise extent.

surface of the left occipital lobe show that the lesion pierces just behind the anterior margin of the striate cortex and penetrates to the posterior branch of the internal parieto-occipital sulcus. It lies slightly in front of the anterior branch of the calcarine fissure just touching the striate cortex on its anterior margin. The cortex on the inferior wall of the internal parieto-occipital fissure is only slightly damaged

(fig. 12). The lesions of the left pre- and post-central convolutions of this animal are described in another paper of this series (Walker, in press.).

Left lateral geniculate body.— Careful examination of the serial sections reveals degeneration only in the middle third of the left lateral geniculate body. Approximately at the oral extremity of its posterior third, degeneration appears in the outer three or four layers along the medial border of the geniculate body. Anteriorly this zone enlarges but becomes slightly more laterally situated, a small portion of the normal lateral geniculate body appearing along the medial border. At this point the zone of wedge-shaped degeneration involves the outer five layers of the geniculate body. Further anteriorly it decreases in size and is confined to the second layer. At its anterior extremity, slightly oral to the middle of the lateral geniculate body, it involves only the second layer (fig. 13).

FIG. 13.—Representative serial sections of the left lateral geniculate body of chimpanzee Ghandi showing the extent of the retrograde cell degeneration.

III.—DISCUSSION.

Cortical projection of the lateral geniculate body.

The cortical receptive area for the visual radiation has been known for many years. Indeed, the unique characteristics of the striate region first directed the attention of histologists to the differences in the minute structure of the cerebral cortex. When the significance of cytoarchitectonics was still a matter of speculation, investigators suggested that the striate region was the seat of cortical representation of visual activity. But it required years of investigation by numerous workers to prove this thesis. Further clinical and experimental studies were necessary to determine the arrangement of the visual projection upon the striate cortex. For this information we are largely indebted to Henschen (1924), Gordon Holmes (1918), Brouwer (1936) and others and to the confirmatory studies of Brouwer and Zeeman (1935), Poliak (1932, 1933) and Le Gros Clark and Penman (1934).

The results of the present investigations supplement these previous studies. It may be assumed on the basis of clinical cases and experimental studies of Spence and Fulton (1936) in the chimpanzee that the posterior pole and lateral surface of the striate cortex represents the macular cortex. In the present research two lesions in this region were studied, both in the upper half of the occipital pole. The first (Experiment 1, right cerebral hemisphere) lies along the posterior margin of the striate cortex and has given rise to degeneration in the medial and posterior part of the lateral geniculate body. The second (Experiment 2, left hemisphere) is located slightly more anteriorly on the margin of the striate area and the resulting degeneration is along the medial margin of the lateral geniculate body but slightly more anteriorly placed.

From these two experiments certain general deductions may be made concerning the arrangements of the visual projection to the striate area. That both lesions were above the calcarine fissure and the degenerations in both cases were in the medial portion of the lateral geniculate body is in accord with the previous findings in both man and animals, i.e., *the medial half of the lateral geniculate body projects to the upper lip of the calcarine fissure.* The second deduction concerns the arrangement of the visual radiation. Both lesions damaged the margin of the striate cortex, and produced retrograde cell degeneration along the medial corner of the lateral geniculate body. This favours the suggestion that the borders of the striate cortex receive their afferent fibres from the margins of the medial geniculate body, and conversely that the cortex on the trough of the calcarine fissure derives its afferent geniculate fibres from the middle portions of that nucleus. Moreover, the lesion at the caudal pole of the striate area gave rise to degeneration more posteriorly than the lesion slightly more anteriorly placed. This observation indicates that the more posterior parts of the lateral geniculate body tend to project to the posterior parts of the striate cortex. This spatial relation is further clarified by a comparison of the degeneration in the lateral geniculate body of Experiment 1 with the changes in the same nucleus in Poliak and Hayashi's (1936) chimpanzee, which suffered a less extensive occipital lobectomy (more striate cortex being spared along the anterior portion of the calcarine fissure). The degeneration in this animal does not extend as far anteriorly in the lateral geniculate body as that in Experiment 1 of this study, and the degenerated sectors at each level are smaller.

With this information it is possible to illustrate schematically the projection of the lateral geniculate body upon the striate cortex of the occipital lobe (fig. 14). In this diagram the retinal projection upon the medial geniculate body and the striate cortex has been included by reference to the

work of Gordon Holmes (1918), Brouwer (1936), and Le Gros Clark and Penman (1934). It is apparent from this diagram that a lesion along the upper or lower margin of the striate cortex would cause retrograde cell

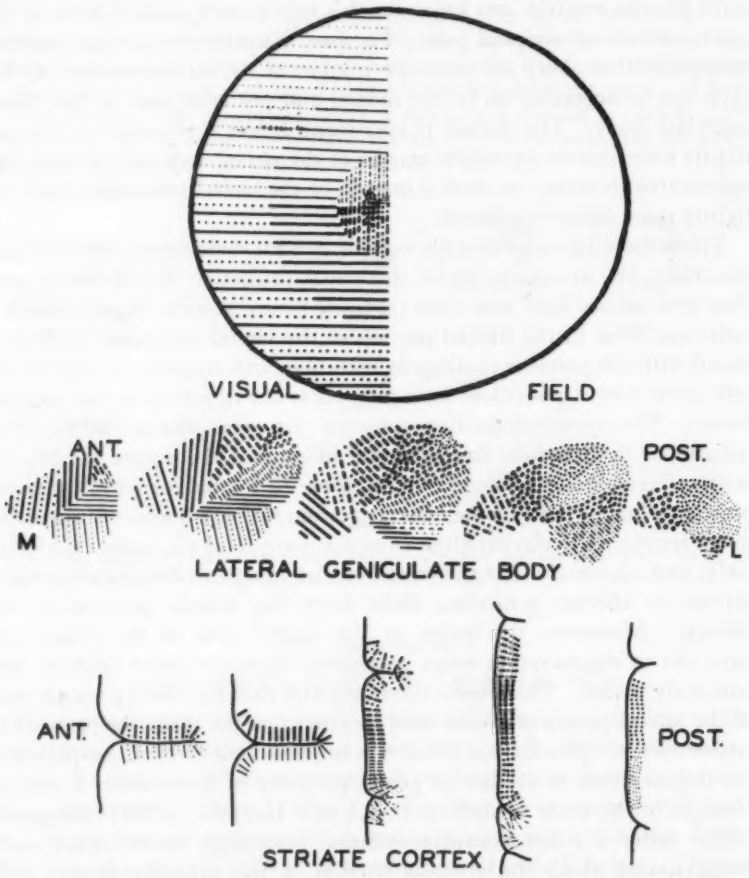

FIG. 14.—A schema to show the projection of the lateral geniculate body upon the striate cortex as determined by this investigation, and the retinal projection upon the lateral geniculate body and striate cortex on the basis of previous investigations.

degeneration in the medial or lateral portion of the lateral geniculate body. It is also evident that the more anterior parts of the lateral geniculate body send their fibres to the more anterior portions of the striate cortex. The

manner of " figure " projection described by Poliak becomes apparent from this schema.

The degeneration in the lateral geniculate body following a large temporal lobe ablation would be difficult to understand if the path of the visual radiation were unknown. But many clinical observations have shown that the course of the geniculostriate fibres is through the temporal lobe. The site of degeneration in the lateral geniculate body following the temporal lobe ablation corresponds with portion of the nucleus projecting to the inferior lip of the anterior part of the calcarine fissure. Involvement of this portion of the visual radiation would be expected to give rise

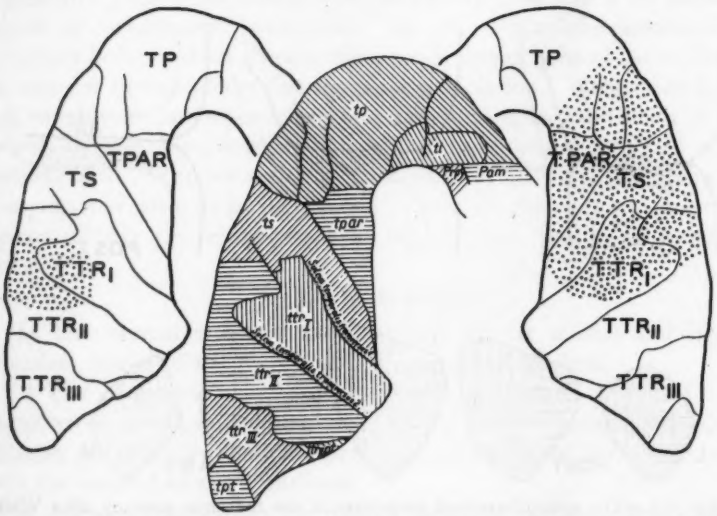

FIG. 15.—The myeloarchitectural fields of the Sylvian region in the chimpanzee after Beck, and the present lesions plotted on this areal map. At the left the lesion in Experiment 1 and at the right that of Experiment 2.

to a superior quadratic defect in the visual field. Clinically Bailey (1933) and many others have shown that such a defect is a common occurrence with tumours of the temporal lobe. Actually the degeneration in the lateral geniculate body in Experiment 2 following the temporal lobe lesion was quite different from that following an occipital lobe injury (compare fig. 1 and fig. 9). The patchy degeneration of the lateral geniculate body in the first instance probably indicates that the component parts of the visual radiation do not maintain an exact constant relationship throughout their course, and that there is some intermingling of the fibres.

Cortical projection of the medial geniculate body.

In spite of much investigation, the central auditory radiation is not clearly understood. That the temporal cortex is the central representation of the auditory system has been generally accepted for many years. Histological studies of the cytoarchitecture of this part of the brain led Campbell (1905), Brodmann (1909), von Economo and Beck to the conclusion that the transverse temporal convolution of Heschl was the primary auditory centre. The early investigators were unable to describe comparable receptive zones in the lower primates and carnivora, although recently Beck (1938) has suggested that such a cytoarchitectural area

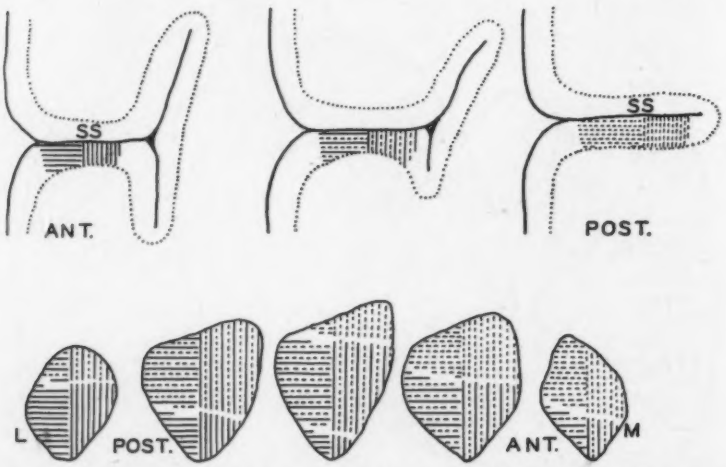

FIG. 16.—The geniculocortical projection in the macaque monkey after Walker. The projection of the medial geniculate body is to the similarly marked portion of the auditory koniocortex.

probably is present in the monkey. Poliak (1932) inclined to the same idea from his experimental studies. Walker (1937) has described an area of auditory "koniocortex" in the macaque monkey limited to the superior surface of the first temporal convolution. For the chimpanzee Beck has described in detail the myeloarchitectural structure of the Sylvian region (fig. 15). The first transverse temporal convolution in this animal is rudimentary, and Beck believes that the central auditory projection area is not confined to it but extends further posteriorly (including TTR I, TTR II, and TTR III).

The present investigation lends support to a more restricted localiza-

tion of the auditory projection area; the experiments are, however, still insufficient for a detailed analysis of its exact boundaries or spatial organization of the radiation. Certainly the fact that a small localized lesion of the superior surface of the temporal lobe produces an extensive zone of retrograde cell degeneration in the corresponding medial geniculate body, is strong evidence in favour of a focal auditory projection area. It is difficult to assess the degeneration of the medial geniculate body in the second experiment because part of the change is probably due to interruption of the auditory radiation and not to primary damage of the auditory "koniocortex." For this reason, it can only be concluded that the degenerated parts of the medial geniculate body projected to the posterior portion of the auditory "koniocortex" (fig. 16). The medial portion of the geniculate body sends its fibres to the inner or deeper parts of the cortex on the superior surface of the first temporal convolution. Walker concluded that roughly an anteroposterior plane projected upon each point of the cortex. By this means intricate integrations could be accomplished at the thalamic level. Whether such a schema will hold for the projection in the chimpanzee remains to be determined. Certainly the auditory projection appears to have precise topographical organization throughout its entire course.

IV.—Summary.

(1) The normal structure and histology of the medial and lateral geniculate bodies of the chimpanzee are described in detail.

(2) The degenerations in the lateral geniculate body of two chimpanzees resulting from lesions of the striate cortex and visual radiation are described, and the projection of the lateral geniculate body upon the cerebral cortex is analysed.

(3) The degenerations in the medial geniculate body are described in two experiments following temporal lobe lesions. The observations indicate that the auditory projection area of the chimpanzee is probably sharply restricted as in the monkey, to a small area on the superior surface of the first temporal convolution, being largely hidden within the Sylvian fissure. The spatial organization of the projection is not yet determined.

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THE TONIC FOOT RESPONSE TO STIMULATION OF THE SOLE: ITS PHYSIOLOGICAL SIGNIFICANCE AND DIAGNOSTIC VALUE.

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(New York).

THE following responses to stimulation of the sole of the foot are usually distinguished: (1) *the normal plantar flexion reflex* of the toes in response to a moving tactile stimulus, followed by a quick return of the toes to normal position; (2) *the pathological, or Babinski plantar response.*

There remains another reflex phenomenon which has not hitherto received adequate consideration: namely, the slow tonic plantar flexion and adduction movement of the toes, with hollowing of the sole and some wrinkling of its skin.

This phenomenon, which we shall speak of as *the tonic foot response,* belongs to that group of tonic responses first described under the name of tonic innervation by Liepmann (1900), Goldstein (1909) and by Kleist (1932). Subsquently, examples of a tonic response to stimulation of the palm of the hand have been recorded under the title of "tonic innervation" by Wilson and Walshe (1915), "forced grasping" by Schuster (1923), Schuster and Pineas (1926), Adie and Critchley (1927) and by others. On the basis of their own observations Walshe and Robertson (1933) reached the conclusion that in the complex phenomena thus named two separable and distinct components are present: (a) "volitional grasping movements" in response to objects seen, or felt in the palm, and (b) "reflex tonic grasping" in response to stretch of the flexor muscles of the digits.

In a later publication Walshe and Hunt (1936) confirmed this view and concluded that the first (grasping movement) component is determined by mental factors, while the second (tonic grasp) is "exclusively a proprioceptive reflex reaction to stretch." Such a distinction had not been made by earlier observers though it is one of importance in understanding the nature of the phenomenon, with the result that the subject was involved in some obscurity.

[1] (From the Columbia University and Montefiore Hospital, New York.) The author wishes to express his appreciation to the Rockefeller Foundation for special grants aiding him in this study, which was carried out under the auspices of the Harry H. Strauss Neurological Fund.

A general discussion of this problem is not now proposed here, but some new observations concerning the tonic component, especially the tonic foot response, will be recorded.

Schuster and Pineas were the first to observe it in the foot and called it "foot grasping." Later it was described by the present writer (1931), by Sittig (1932), by Freeman and Crosby (1929) and Russell Brain and Curran (1932).

Following the case reports there will be a theoretical discussion and a consideration of the diagnostic significance of the phenomenon.

Case Reports.

Case 1.—A. R., a woman aged 21. She complained that for over two months she had developed a progressive weakness of the right side, sensory impairment in the right leg and severe left-sided headaches. On examination there was a right hemiparesis. The right hand showed defect of two-point discrimination and of appreciation of size and shape. There was also postural sensory impairment in the right arm. The tendon reflexes on the right were increased and the right plantar response was of the Babinski type. The right abdominal reflexes were absent. There was no tonic foot response.

There was exophthalmos of the right eye and bilateral papillœdema. A diagnosis of left parietal lobe tumour was made.

At operation a cyst was found in the sub-cortical region of the parietal lobe, 4 cm. from the mid-line on the left side. The cyst wall was dissected out and was later reported as glioblastoma multiforme. Two days after the operation, the patient complained of severe headaches and general weakness. The pulse rose from 88 to 120 and the temperature from 98° to 99·4° F. At that time, she had a clear-cut tonic plantar response on the left foot. No other pathological signs were seen on the left side. Right-sided symptoms were as before. After two days, during which the patient improved a great deal generally and the temperature and pulse returned to normal, the tonic foot response disappeared and was not subsequently observed during a period of some 11 months.

Since there was no evidence of a lesion of the right hemisphere we might at first glance assume that the tonic foot response is a homolateral phenomenon. However, a closer observation of the relationship between the onset and disappearance of the phenomenon and the general condition of the patient led us to consider the phenomenon as an expression of a functional derangement of the contralateral hemisphere. The phenomenon was only observed during the immediate post-operative period, that is, when the operated hemisphere was œdematous. We may assume that the œdematous hemisphere compressed the other hemisphere and thus disturbed it functionally. If this be so, we may relate the tonic response to this functional damage of the hemisphere contralateral to the limb where the phenomenon was observed. The fact that this tonic response was observed without any

other abnormal sign on this side, notably without any pyramidal tract symptoms, leads us to regard it as an expression of but slight disturbance of cortical function. This case is not suitable for localizing the phenomenon in relation with any special region of the brain, but subsequent cases will show that the frontal lobe seems to be especially important in this respect.

Case 2.—J. G., a male, aged 42. Brain abscess.

Eight weeks' history of sinus infection followed by headache on the right side of the head, progressive weakness and sensory loss of the left face, arm and leg.

On examination there was a central type of weakness of the left side of the face, tongue and soft palate, flaccid left hemiplegia with increased tendon reflexes, transient ankle clonus and Babinski plantar response. All forms of sensation were impaired in the left side, and in the left hand postural sensibility and stereognosis were absent. A right frontal lobe abscess was diagnosed.

At operation the abscess was found in the posterior part of the middle frontal convolution. Three months later a second operation was performed to secure adequate drainage. The patient remained in bad general condition for some months, and after this period the physical signs were as follows: confusion, defective attention and memory for recent events, a strong sucking response to tapping of the *right* side of the mouth, a flaccid left hemiplegia with increased tendon reflexes, a variable Babinski plantar response. There was no forced grasping of the hand, but touching the *right* sole evoked plantar flexion of foot and toes which persisted for some time. The toes then slowly dorsiflexed and made quick alternating dorsal and plantar flexion movements. Of these dorsiflexion was the more rapid and became longer-lasting each time. Stimulation of the *left* plantar response also elicited this tonic response of the right foot.

Three weeks later the general condition was markedly worse. The tonic plantar response of the right foot was not so well-marked as previously. A bilateral Babinski response was obtained, and a grasping response of the right hand. The sucking response was present as before. A few days later the general condition became progressively worse, there was early papillœdema and the patient died with symptoms of meningitis.

Post-mortem examination.[1]—The right hemisphere was larger than the left and its convolutions were all flattened. The superior longitudinal sinus was shifted to the left, especially in the frontal region. There was a slight bulging of the right gyrus cinguli compressing the left hemisphere. The right lateral ventricle was constricted, the left slightly dilated. There was an irregularly shaped abscess in the region of the right insula. The temporal horn of the right ventricle was dilated, the third ventricle was obliterated and contained a little pus. There was pus within the horns of the right ventricle. The left hemisphere itself was not involved by the abscess.

In this patient with a right-sided brain abscess we found left-sided pyramidal tract symptoms and a tonic foot response on the right side.

[1] The author is indebted to Dr. Charles Davison of the Neuro-Pathological Laboratories of the Montefiore Hospital for the gross and microscopic pathological reports, and the permission to use these reports.

The clinical facts may be interpreted as follows: as long as the abscess in the right frontal lobe did not press upon the left hemisphere the symptoms were confined to the left side of the body. Later, when the process in the right hemisphere increased and this hemisphere was swollen, the tonic foot response appeared as the first sign of pressure on the left hemisphere. With the increasing disturbance of the left hemisphere, a Babinski response also appeared on the right side, simultaneously with some decrease of the tonic foot response. At this point forced grasping and groping responses of the right hand and a sucking phenomenon of the right side of the mouth appeared. We are inclined to explain these phenomena in the following way. The tonic foot response is the first sign of functional derangement. With an increase of this the Babinski appears and may to some degree mask the tonic response. Later we shall see that both phenomena may be observed at the same time. The grasping of the hand may be considered as an expression of more severe disorder. The autopsy reports confirmed our assumption by the fact that the right hemisphere was greatly enlarged, and, by pressure displaced the left hemisphere. The relationship between the tonic response and the frontal lobe was also confirmed.

Case 3.—H. R., male, aged 30.

History.—Two and a half years previously the patient was noted to have a fit while asleep. There was stiffness of the extremities and shaking of the entire body for five minutes, then a deep unconscious sleep from which he could not be roused. These fits recurred at intervals of three to four months. The fits subsequently became more frequent and were later accompanied by headaches and vomiting. Vision was then noticed to be failing. The clinical diagnosis was tumour of the right frontal lobe.

Operation revealed an astrocytoma of the right frontal lobe. This was treated by X-ray therapy.

Neurological examination.—Six months later, the patient tended to fall asleep, was apathetic and unresponsive, disoriented, and showed a memory defect both retrograde and anterograde. Evidence of motor asphasia and of apraxia of the left extremities were observed. There was incontinence of urine. The left arm deviated and was coarsely tremulous, there was some weakness of the left side of the face and nystagmus on deviation to the left, with some weakness of right lateral deviation of the eyes. The left tendon reflexes were increased, the left upper abdominal reflexes absent, the lower feeble. The left plantar response was of the Babinski type. *Tonic plantar response to pressure on the right foot. Slight grasping in the right hand.* Bilateral sucking and biting responses to stimuli, right greater than left. The patient gradually got worse and died.

Post-mortem.—Right hemisphere larger than the left. The right frontal convolutions were flattened and apparently infiltrated by a neoplasm. The ventricles were filled with tumour tissue and were enormously dilated. The ependymal lining of the right ventricle was distorted and infiltrated by tumour tissue. Part of the tumour invaded the centrum ovale in the region of the inferior parietal convolutions. Cystic degeneration or porencephalic destruction was found in the white

matter of the first and second frontal convolutions on the right. The corpus callosum was also partially infiltrated by the neoplasm. The tumour infiltration extended back into the anterior nucleus of the thalamus, the splenium of the corpus callosum and right hippocampus, septum pellucidum, fornix and left hippocampus. Hæmorrhagic areas were found throughout the thalamus, in the left dentate nucleus extending into the region of the left superior peduncles.

The lesion was in the right fronto-temporal region with pyramidal tract symptoms on the left side of the body. With an increase of the process there appeared a tonic plantar response on the right foot and a slight grasping of the right hand.

This case also reveals the connection of the tonic foot response with a functional disorder of the anterior part of the brain opposite the site of the lesion.

FIG. 1.

Case 4.—J. B., female, aged 40.

History.—She complained of "splitting" right-sided headaches for four or five months, ceasing spontaneously and reappearing one week after delivery of a child in the early part of May, 1935. She vomited and became confused and delirious on May 18, 1935, and continued in a state of mental confusion, somnolence and restlessness. Later she fell into a stupor.

On examination, she was acutely ill, showing bilateral papillœdema, bilateral 6th nerve weakness and left facial weakness. There was generalized hyper-reflexia.

The clinical diagnosis was tumour of the right fronto-parieto-temporal region. Operation on October 6, 1935. A deep sub-cortical glioma in right fronto-temporal

region with a cyst was found. One year later, exposed to intensive X-ray therapy without improvement.

Neurological examination a year after operation revealed a left hemiparesis with increased tendon reflexes on both sides, especially on the left. There were bilateral Babinski plantar responses and bilateral tonic foot responses. Emotionally she was unstable, varying from euphoria to tears. She was restless, speech was indistinct and attention defective, though memory was fairly good. There was left homonymous temporal hemianopia.

Tonic foot responses were elicited bilaterally; there was a sucking response on the left side of the mouth and grasping of the left hand. She went progressively downhill and died.

Post-mortem (Brain) (Fig. 1).—Flattening of practically all the convolutions of the right hemisphere. Right gyrus cinguli bulged slightly into the left gyrus cinguli. The brain stem and cerebellum as well as the right cerebral peduncle were pushed to the left. Marked œdema of the white matter of the right hemisphere with a constriction and slight dilatation of the right lateral ventricle. The right internal capsule was more prominent than the left. The thalamus and basal ganglia were compressed on the right. A tumour nodule was seen in the region of the temporal lobe and involving also the hippocampal and fusiform gyri. It was cystic in part of the inferior parietal convolutions.

This patient was especially interesting because she showed the Babinski and the tonic response at the same time. That these two phenomena are unrelated seems clear since they were elicited by different stimuli, a slight moving stimulus especially at the base of the toes evoking the Babinski response, while touch or pressure to the sole produced the tonic response. Further, this patient showed on stimulation of one side, the right, a tonic response on both sides.

From the post-mortem examination we are justified in assuming that the tonic response on the right side was due to the pressure on the left hemisphere, produced by the tumour in the right hemisphere. We may assume further that the tonic response was produced by the lesion of the frontal lobe, the Babinski by that of the motor area.

Case 5.—H. K., male, aged 55.

History.—Illness began in January, 1936, with frontal headaches, vertigo, blurred vision and subsequent left-sided hemiplegia.

Operation for a right frontal neoplasm, followed by deep X-ray therapy. Headaches disappeared and movements of the left arm and leg returned. In May, 1936, headaches and left hemiparesis returned with periods of unconsciousness. Some years previously he had been treated for lead poisoning, and had had tremors of both hands since that time.

Neurological examination.—Mental retardation, psychomotor restlessness and emotional instability. Slight bilateral papillœdema with secondary optic atrophy on the left. Left hemiplegia, left hemihypesthesia with astereognosis, fine tremor of the outstretched right upper extremity, uncertain and partial left homonymous field

defect. Absent abdominal reflexes, tonic plantar response of the right foot, protrusion of lips to touch on right side of mouth. Course was progressively downhill and the patient died.

Post-mortem examination.—Right hemisphere slightly smaller than the left, dura adherent to the first and second frontal convolutions. Area of necrosis in white matter of right hemisphere, near the anterior tip of lateral ventricle. All frontal convolutions, except orbital, were obliterated. White matter markedly anæmic in frontal area of right hemisphere. Tips of frontal convolutions showed a necrotic zone and abscess-like area which communicated with the tip of the right lateral horn. Microscopic diagnosis: Astrocytoma.

Summary: Right frontal neoplasm, left sided symptoms were the first signs. Later there was a tonic plantar response of the right foot and a tonic response of the mouth musculature to tapping on the right side. Here the relationship between the functional disturbance of frontal lobe and the appearance of the tonic foot response on the side opposite the lesion is clear.

Case 6.—A. S., male, aged 30.

History.—For two years he had " difficulty " with his right eye and some twitching of the right side of the face, which at the end of this period spread to the hand and foot of the right side. At this time, also, there were severe right-sided headaches accompanied by dizziness and blurred vision. Later, he had a convulsion lasting for three hours and consisting of twitching of the right side, frothing at the mouth, tongue-biting and incontinence. There then developed memory defect, aphasia and an increase of convulsions to three daily. He was operated on twice, to relieve pressure and to remove a cyst, but the symptoms returned. Two further operations were followed by X-ray therapy. This led to a slight improvement, but was followed by a downhill progress.

Diagnosis was glioblastoma of the left fronto-parietal area.

On return to hospital, marked irritability and a tonic plantar response of the left foot. Grasping response in the left hand with an after-groping in the right hand. There was only a slight grasping response of the right hand. A tonic foot response was elicited to tapping on the right side, and there was a sucking response to lip stimulation. Two weeks later there was no tonic plantar response, only a slight grasping in the left hand with no after groping of the right hand, and no grasping in the right hand. The patient became much more cheerful and co-operative and showed marked improvement, and left the hospital.

In this case there appears the same relationship between a functional disturbance of the cerebral hemisphere by pressure and the tonic foot response on the side corresponding to the affected hemisphere. With a decrease of the primary process and improvement of the general condition and, as we may assume, a decrease of pressure on the opposite side, the tonic response disappeared.

This case showed other interesting phenomena. There was bilateral tonic grasping of the hands. With improvement in the patient's general condition this grasping diminished more on the side opposite the tumour than on the other side.

Case 7.—A. H., housewife, aged 52.

History.—For seven years she had been subject to "spells" in which she did not lose consciousness, but talked incoherently, was confused and convulsed on the left side. The twitching begins in the foot and spreads to involve the entire left side, including the face. The attack is preceded by a feeling of weakness of the left side, and is followed by transient weakness of that side. Sometimes the aura is not followed by an attack, and sometimes she is able to keep off an attack by squeezing the left hand with the right, for in the aura the fingers of the left hand spread wide apart. On the advice of her doctor she ceased work for sixteen months, during which time the attacks ceased, only to recur when she resumed work.

On admission to hospital the following signs were noted: The visual fields were normal. There was blurring of the nasal margin of the right optic disc and bilateral fullness of the retinal veins. She was normal mentally. There was a slight left hemiparesis, face, arm, leg, the leg being weaker than the arm. There was slight inco-ordination of the left hand and arm. The tendon-jerks were increased on the left, and there was a doubtful Babinski response on plantar stimulation of that side, but on stroking the skin below the external malleolus a more definite extensor plantar response was obtained. There was no sensory loss. A radiogram showed enlargement of the sella with thinning of the dorsum and posterior clinoid processes. A faint cloud-like shadow in the right frontal region suggested the possibility of calcification in a tumour. The encephalogram revealed displacement of the ventricular system to the left, with downward displacement of the right lateral ventricle, which was deformed posterior to the plane of the foramen of Monroe.

A provisional diagnosis of right frontal tumour was made. At operation no abnormal appearance was seen and no tumour found. Needle punctures gave a negative result. Two days following operation, the patient had two left-sided seizures followed by a flaccid hemiplegia. This slowly improved and tended to become spastic. She was discharged to the clinic one month after the operation.

Neurological examination (1937).—Since the operation, the symptoms are essentially as before, there is a left hemiplegia with spasticity of the extremities, and in the past two years the patient has been able to walk without a stick. Headaches have occurred, but not very severe, "like a band across" frontally and bilaterally. In the past few weeks, there has been some nausea but no vomiting. Hearing is diminished in the right ear (past six months). Intelligence shows marked change, similar to that commonly found in frontal lobe involvement, and attention is poorly sustained. Tendon hyper-reflexia is marked on the left, slight on the right. There is a Babinski response on the left and a tonic plantar foot response on the right. There is a tendency to slight tonic grasping in the left hand. Abdominal reflexes are diminished on the right, absent on the left. Retinal arteries are enlarged and veins engorged. The disc margins are blurred, but visible, and there is some atrophic pallor of the left disc.

In this case a suspected tumour of the right frontal lobe produced symptoms of a left hemiplegia. In addition, there was to be observed a tonic plantar foot response on the right side, as well as a faint grasping of the left hand. We may explain the tonic foot response as a sequel to the pressure of a right sided tumour on the left frontal lobe. The faint grasping in the left

hand is assumed to be a symptom of the increasing infiltration of the neoplasm in the right frontal lobe.

II.—Discussion on The Origin of the Tonic Foot Response.

As Brain and Curran have described, the phenomenon is to be elicited by direct pressure upon the sole without a moving stimulus. I should like to add that in my experience an increase of the pressure, especially to the ball of the foot, leads to an increase of the response. Painful stimuli are similarly effective. The stimulus differs from that by which the Babinski response is elicited, the latter being produced by a stroking of the sole. It differs also from the stimulus by which the normal plantar response is elicited, which also consists of a light stroking.

The tonic phenomenon consists of a flexion and adduction movement of the toes, associated with a curving of the foot and wrinkling of the skin of the sole. It looks like an " Umklammerung," or clasping of the stimulating object (fig. 2).

Sometimes this is seen clearly when a pencil is placed at the base of the toes. The toes grasp the pencil. The movement is slow, the contraction persists with the stimulus, and also for a varying time after stimulation. It increases with continuation of the stimulus. Relaxation after removal of the stimulus takes place slowly in short jerks. The reaction has a very strongly forced character and in some cases cannot be inhibited by the subject. In individual cases there may be differences as to the duration and intensity of the reaction and as to the control of the individual over it.

This reaction has been found[1] to coincide with the finding of *damage of the frontal lobe* or of efferent fibres from this part of the brain. Lesions involving the medial aspect of the frontal lobe seem especially prone to produce it. Signs of a lesion of the pyramidal tracts (the motor area) may co-exist with the tonic response, but they are not related. This may be verified by the fact that they are to be elicited by different stimuli. Sometimes severe pyramidal tract lesions seem to cover or mask the tonic response. The tonic response is a sign of slight damage of the frontal lobe, of which it seems to be the first expression. Therefore, it is to be observed not seldom on the side homolateral to an expanding lesion of the brain,

[1] Observation of a large number of patients during *insulin treatment* showed that a markedly developed tonic foot response is a very common finding in this condition. The phenomenon appears relatively early and remains for a very long time. If the Babinski is present, sometimes the former phenomenon disappears, or, at times, both reactions can be elicited. The tonic foot response is frequently accompanied by a grasping in the hands and by a tonic phenomenon of the lips.

FIG. 2.

namely, when there is involvement of the opposite side by pressure. The tonic foot response is essentially a contralateral symptom, but its homolateral appearance is particularly characteristic of brain tumours. If the causative involvement of the frontal lobe increases, especially if it should involve the more lateral regions of this lobe there also appears a tonic response in the hand, and a tonic response in the lips of the same side.

III.—The Nature of the Tonic Foot Response.

There is no doubt that the tonic foot response is of a similar character to the tonic grasping of the hand. Our conception of the nature of the tonic foot response is therefore determined by our conception of the tonic grasping of the hand. The latter has usually been considered as a release of a phylogenetic reflex or as a compulsive normal grasping, or as a grasping reflex of infants, inhibited in adults. That this phenomenon is not caused by the reappearance of a subhuman reflex is to be seen in the fact that tonic foot-grasping, according to the investigation of Brain and Curran, is not observed either in (adult) monkeys or in anthropoid apes.

As I have explained elsewhere (1931), the so-called forced grasping of the hand has nothing to do with the normal grasping of adults, but is a pathological phenomenon, an expression of an abnormal reaction to stimuli, corresponding to reactions characteristic for parts of the nervous system isolated from the higher centres. As I have suggested (1936), every reaction of the organism starts with a turning-to movement of the organism towards the stimulus object, by which the organism achieves a connection with this object. Normally, this first step is followed by the reaction corresponding to the task which the situation demands and therefore represents only a short transient part of the reaction. Under some pathological conditions this " turning-to " movement appears isolated and gains by this isolation an abnormally forced appearance. This is to be observed especially in lesions of the cerebellum and frontal lobe. One expression of this abnormal " turning-to " reaction is the so-called forced grasping of the hand. I believe the same is the case in the tonic plantar response of the foot. With this consideration it is intelligible that a very simple stimulus such as pressure or touch is sufficient to elicit the reaction, and, further, that an increase of the stimulus leads to an increase of the reaction. The fact that this tonic response is also elicited by disagreeable stimulation makes it appear very unlikely that forced grasping has anything to do with normal grasping. The normal individual is not inclined to grasp disagreeable objects. Therefore the phenomenon should not be called forced grasping but rather an *abnormally forced " turning-to " movement.*

FIG. 3.

That the phenomenon under discussion has nothing to do with the grasping of an object, but represents a forced turning toward the stimulus, is to be seen in an observation which may be made in some patients with so-called forced grasping of the hand. If, instead of the palm, the dorsal side of the hand be stimulated, then we may observe a movement of the same forced character, directed not palmarward but dorsally (fig. 3). Such a reaction cannot have anything to do with grasping but is intelligible on the same principle as the so-called grasping, namely, as an expression of an abnormal " turning-to " movement towards the stimulus. One particularly clear example of the dorsal reaction has been published in my former clinic by H. Cohn (1930).

I have seen a corresponding phenomenon in the foot in a case of tonic foot response. On stimulating the dorsiflexors of the toes, after a certain time there appeared a slow dorsal movement of the toes, especially of the big toe, increasing with the continuation of the stimulus and persisting for some time after its cessation.

The so-called forced grasping also has nothing to do with the very intense grasping of children. However, in early childhood, we may observe a forced clasping of the hand which disappears gradually as the child learns to use his hand, i.e. becomes capable of real grasping. This forced clasping corresponds to the pathological grasping, so-called forced grasping of the adults. It is an abnormal " turning-to " movement. It corresponds to the isolation of the function of the concerned brain centres, as a result of the immaturity of the higher centres in early childhood. For the same reason we observe a tonic foot response in children and its disappearance later than the phenomenon in the hand is intelligible because the child only learns later to use his foot for a purposeful movement. Brain and Curran have observed that the tonic response does not usually disappear before the ninth month of life, sometimes much later. My observations lead me to agree with these authors and with the similar description of the phenomenon which Sittig has given. The latter's observations accord with those of Brain and Curran as to the presence of the tonic foot response in young monkeys—but not in adults. This view of the tonic foot response makes it easy for us to understand that patients who present the tonic foot or hand phenomenon also present a similar type of phenomenon of the lip: this has usually been called a sucking reflex. I shall not discuss here whether there is such a thing as a true reflex in adults corresponding to the sucking of an infant. The phenomenon under consideration is not related to sucking. This becomes clear since we are able to observe the phenomenon on one side only. A tap on the lip is followed by a unilateral pouting movement and closing of the lips, a pattern which does not correspond to sucking. It cor-

responds to the other forms of tonic response to stimulation, in the sense of a " turning-to " movement, and is only another expression of this.

IV.—The Diagnostic Significance of the Tonic Foot Response.

As we have seen, these tonic responses appear as the first signs of an involvement of the anterior part of the cortex, especially of the frontal lobe, even earlier, as I believe, than the Babinski sign or other pyramidal tract signs. Therefore they possess a diagnostic value for a lesion in this region. The tonic response of the foot arises especially with a lesion of the medial part of the frontal lobe, and a lesion which involves the lateral parts of this region is also followed by tonic hand grasping and a tonic lip response. Should these phenomena be combined with pyramidal tract signs, we may then assume an associated lesion of the motor area. The tonic foot response is of special interest in cases of brain tumour since its appearance on the side homolateral to the tumour allows us to assume that the disease process has taken on a progressive character and presses upon the crossed hemisphere. Thus it may well be the first sign of œdema of the brain after operation for a tumour.

Summary.

(1) This study is concerned with the tonic response of the foot to stimulation of the sole. The character of the reaction is described. It is a slow movement, elicited by touch or pressure to the sole of the ball of the foot. Increasing stimulation, especially if painful, leads to an increase of the movement. The posture persists for some time after cessation of stimulation and then the foot slowly returns to its habitual position.

(2) A relationship is suggested between the tonic foot response and lesions of the frontal lobe. This tonic response is considered as one of the earliest signs of a lesion of the frontal lobe. It appears earlier than the Babinski response or other pyramidal tract signs.

(3) Therefore the tonic foot response has a special diagnostic value, especially when it appears on the side homolateral to a lesion of the frontal lobe. It then indicates that the affection of the one frontal lobe is pressing upon the frontal lobe of the other side or that there has been a spread of the process into the crossed side. It is a symptom which points especially to a lesion of the medial part of the frontal lobe.

(4) The tonic foot response, in the same way as the so-called forced grasping of the hand, is not related to the normal phenomenon of grasping. It is an expression of an abnormal " turning-to " movement of the organism to the stimulus object, and appears as a response of the lower mechanisms when the " higher centres," especially of the frontal lobes, are damaged.

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NOTE ON THE NUCLEUS RUBER MAGNOCELLULARIS AND ITS EFFERENT PATHWAY IN MAN.[1]

BY KARL STERN.

Introduction. Survey of previous literature.

The large-celled red nucleus (n. ruber magnocellularis) has a direct uninterrupted connection with the lower motor neuron through the rubrospinal tract (v. Monakow, 1909-1910). The experimental work on the red

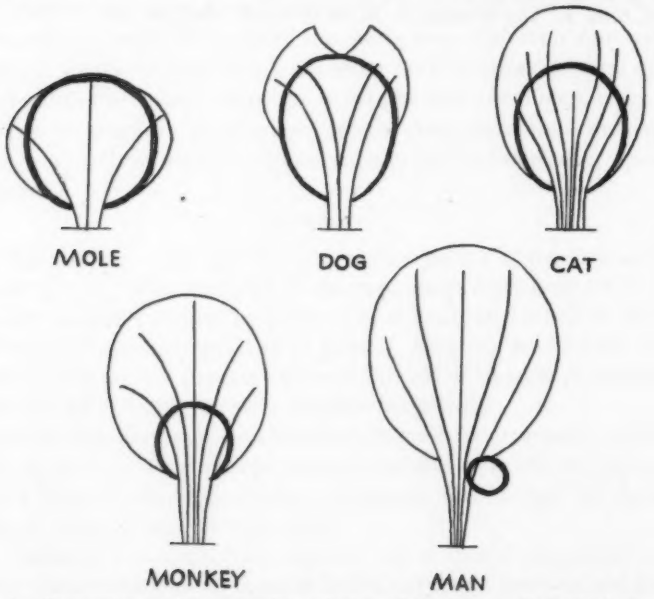

Fig. 1.—Proportion and topographic relation of the large-celled (thick line) and small-celled (thin line) red nucleus in various mammals and in man. The fibres indicate the superior cerebellar peduncle, the horizontal line the level of its decussation. (Schematic drawing, modified after Winkler.)

nucleus (Rademaker, 1926) has been done on those animals in which the large-celled part is the main part and the rubrospinal tract is a prominent bundle. The results of this experimental work can only be applied to

[1] From the Pathological Laboratory of the National Hospital, Queen Square, London.

human physiology if a homologue of the nucleus ruber magnocellularis and a rubrospinal tract exist in man. This, however, has been doubted by recent investigators. The present contribution is an attempt to throw more light on this question.

It is well known that in man the red nucleus is in its cyto-architecture and in its fibre-tract connections a complicated centre and very different even from that of the anthropoid apes (fig. 1). von Monakow (1910) concluded from certain morphological features that a small residuum of

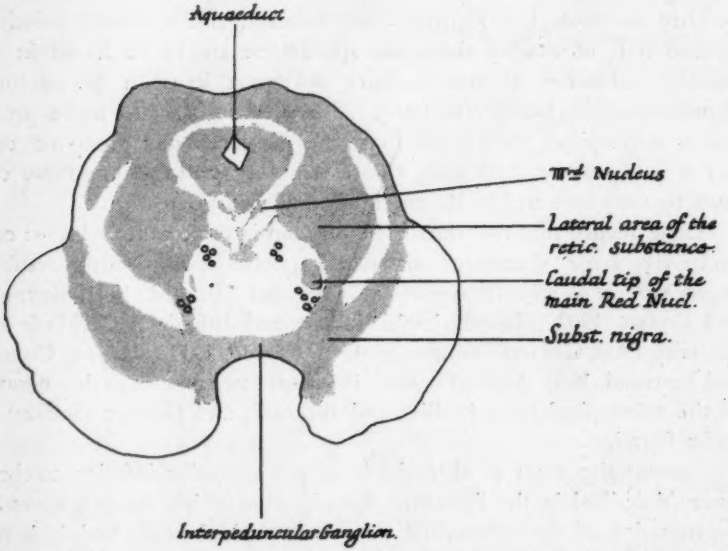

FIG. 2.—The grey formations of the human mid-brain at the level of the caudal tip of the red nucleus. The small circles indicate the position where the few giant motor cells can be found which are regarded as a residuum of the n. ruber magnocellularis. (Half-schematic.)

the n. ruber magnocellularis existed in man. Its position is the level of the "nucleus albus" of Stilling (the brachium conjunctivum oral to its decussation), the caudal tip of the main red nucleus and the transition between the nuclei of the 3rd and 4th nerves. Small clusters of giant cells of a "motor" type may be found in two different places in the cross section (fig. 2). One group is ventral and lateral to the 3rd nucleus, between the latter and the centre of the brachium conjunctivum, the other group is dorsal to the substantia nigra, between the latter and the brachium conjunctivum. This distribution, however, and the size of the

groups vary greatly with different individuals. In a caudo-oral direction they occupy only a short distance and on the average one finds not more than about three cells in one section (Winkler, 1929). In spite of the presence of many elements of the reticular substance and of unpigmented cells of the substantia nigra the cells are easily recognizable. The characteristic way in which they are suspended within the network of the fibres of the 3rd nerve and of the superior peduncle, and their size and Nissl structure made Monakow regard them as the homologue of the large-celled red nucleus.

This morphological identification, however, is not wholly sufficient, because cells of exactly the same appearance are to be found in the reticular substance of the medulla oblongata in man (n. motorius gigantocellularis, Jacobsohn, 1909). Therefore it has also to be proved that a rubrospinal tract arises from the mesencephalic group of cells. It can easily be realized that a fibre tract originating from these cells must be very fine, and its degeneration difficult to detect.

The evidence that this tract exists in man is very scanty. In the comparatively large literature on mesencephalic lesions with resulting degenerations of efferent systems (Collier and Buzzard, 1901, Raymond and Cestan, 1902, Haenel, 1902, Halban and Infeld, 1902, Marie and Guillain, 1903, Gordon Holmes, 1904, H. Claude, 1912, Souques, Crouzon and Bertrand, 1930, André-Thomas, 1936) only two reports of degeneration of the rubrospinal tract (Collier and Buzzard, and Gordon Holmes) are to be found.

Among the cases of thrombosis of the posterior inferior cerebellar artery described in the literature there is none which shows a secondary degeneration of the rubrospinal tract in the spinal cord (André-Thomas, 1936) although its situation in the retro-olivary area would lead us to expect this. Déjérine and Long (1912) in their study of a complete transverse lesion of the cervical cord in man did not see any degeneration of the rubrospinal tract caudal to the lesion.

The opposite method, i.e. to look for retrograde degeneration of the n. ruber magnocellularis, following medullary or spinal lesions appears more promising. It has, however, been used in very few cases (Monakow, 1910, Winkler, 1929). Monakow described a case of cervical syringomyelia in which the cells of the n. ruber magnocellularis had disappeared. Winkler, however, remarks that in such long-standing cases a transneuronal degeneration resulting from lesions of afferent pathways cannot be excluded with certainty.

Gagel (1932) in examining Foerster's cases of chordotomy reported that

PLATE XV.

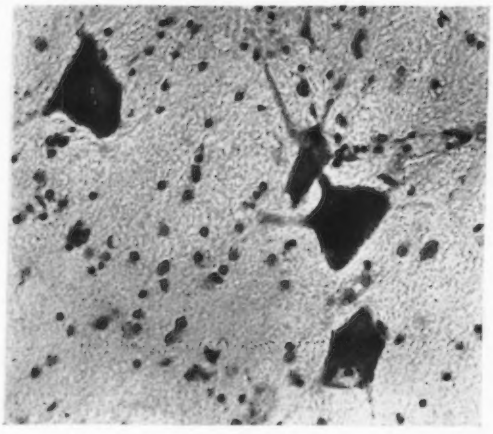

FIG. 3.

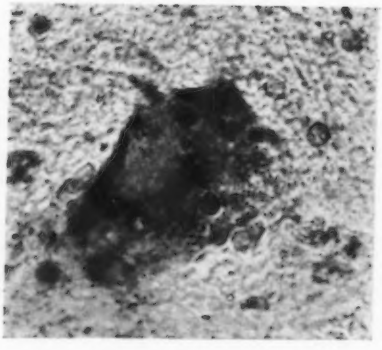

FIG 4*a*.

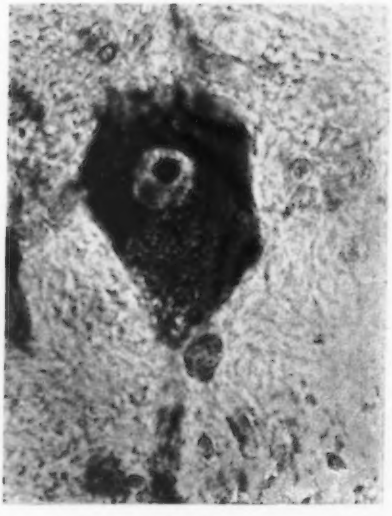

FIG. 4*b*.

FIG. 3. *Case 1.*—Cells of the n. ruber magnocellularis. Typical retrograde cell change. (Nissl. × 200.)

FIG. 4*a*. *Case* 2.—Cell in the n. ruber magnocellularis on the left side. Retrograde degeneration. (Nissl. × 750.)

FIG. 4*b*. *Case* 2.—Normal cell of the n. ruber magnocellularis on the right side. (Nissl. × 750.)

To illustrate Article by Karl Stern.

he did not see any retrograde changes of neurons in the medulla oblongata or mid-brain except in Deiters' nucleus.

André-Thomas (1936) reporting one case of a mesencephalic lesion and reviewing the literature on the same type of case doubts the existence of a rubrospinal tract in man and criticizes the few positive findings.

Personal Observations.

For this investigation two cases were chosen in which (considering the interval between lesion and death) one would expect signs of retrograde degeneration in the cells of the large-celled red nucleus provided there was an uninterrupted pathway.

(1) *The first case* (F. C., P.M. No. 32, 1936) is one of paraplegia from invasion of the spine by a bronchial carcinoma. The patient, a man aged 40, had suffered for six weeks from a feeling of deadness from the chest downwards and from inability to move the legs. These symptoms had developed within three days. He had lost control of his sphincters.

On examination there was complete sensory loss and complete paralysis below the 4th thoracic segmental level. He developed bronchopneumonia and died six weeks after the onset of his neurological symptoms.

Post-mortem examination (Dr. J. G. Greenfield) revealed a bronchial carcinoma with extrathecal spinal metastases. There were carcinomatous masses in the muscles of the right side of the spine between the first and second ribs. The laminæ were soft at these levels. Inside the canal there was a mass at the level of the 2nd thoracic body and opposite the 6th thoracic body. The cord was completely softened from the lower end of the 4th to the 10th thoracic segments. There were a few secondary growths of the size of a split pea in the frontal lobe. The rest of the cerebrum, the cerebellum and the brain-stem were free from secondary growths.

Microscopical examination of the cord in the softened area showed that the softening occupied practically the entire cross section and was most marked centrally.

The microscopical examination of the mid-brain in the area of the large-celled red nucleus by serial sections 15 μ thick and stained by Nissl's method showed a perfect Nissl structure in the cells immediately adjoining the nucleus ruber magnocellularis (e.g. nucleus of the 3rd nerve, substantia nigra, mesencephalic nucleus of the 5th nerve). The glia was normal everywhere. The large-celled red nucleus was represented chiefly in the dorsal area, where cells in every section showed the typical picture of a retrograde chromatolytic change. On the right side the abnormal cells could be seen in clusters (fig. 3), on the left side as single cells and groups of two or three distributed over several sections.

(2) *The second case* (H. B., 1936) was one of thrombosis of the posterior inferior cerebellar artery. A man of 48 suddenly became ill with the typical symptoms of the lateral bulbar syndrome. There was partial loss of use, and gross ataxia and asynergia of his right arm and leg, a complete anæsthesia of the right half of the face, hoarse voice, and a loss of sensation to pain over the left half of the body and

the left limbs. He died fourteen days after the onset of the illness. Post-mortem examination showed an infarction of the right posterior inferior cerebellar artery. The typical triangular retro-olivary area in the medulla oblongata was necrotic with a complete loss of myelin sheaths.

The mid-brain was examined in serial sections (15 μ thick) every fifth and sixth of which were stained. The available blocks extended from the middle of the anterior colliculus down to the "nucleus albus."

Many nerve cells showed a marked degree of lipoid change. Nevertheless the Nissl structure in the cells of the 3rd and 4th nerve nuclei and of the substantia nigra was clear. In a section of the large-celled red nucleus, which in this case lay chiefly in the ventral position, retrograde chromatolytic changes were seen in all the cells on the left side (fig. 4*a*). The cells on the right side were normal (fig. 4*b*). The same difference could be seen in adjoining sections. By staining only the fifth and sixth sections a part of the large-celled red nucleus was unfortunately lost.

The appearance of the main red nucleus was normal. So was the appearance of the field of the reticular substance lateral to the nucleus albus (area parabigemina of Mingazzini) which Winkler regards as another residuum of the "palaeo-rubrum." The nerve cells in this area, however, show normally an irregular Nissl pattern and eccentric nuclei so that retrograde changes cannot be stated with certainty.

From the two cases described we may conclude that the few large motor cells at the caudal end of the red nucleus possess axons which reach at least as far as the upper thoracic cord, that these axons cross above the level of the medulla oblongata and that they pass through the retro-olivary area. This study affords further evidence that a residuum of the "palaeo-rubrum" and a true rubrospinal tract exist in man. On the other hand it demonstrates the extremely small size of this system in man compared with that of the animals commonly used for experiments, and shows how careful we must be in applying the results thereby obtained to the physiology of the human red nucleus.

Summary.

In a case of spinal transverse lesion at a high thoracic level and in a case of thrombosis of the posterior inferior cerebellar artery the n. ruber magnocellularis (v. Monakow) was investigated for retrograde chromatolytic changes. In the first case such changes were present on both sides, in the second case they were confined to the side opposite to that of the lesion. These findings may be regarded as evidence that a rudimentary "palaeo-rubrum" and rubrospinal tract exist in man, a question which is still the subject of discussion in the literature.

I wish to express my gratitude to Dr. J. G. Greenfield for the use of his material and his post-mortem records, and for the suggestions which he gave me during this investigation.

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THE LOCAL SWEAT RESPONSE TO FARADIC STIMULATION.[1]

BY R. W. WILKINS (BALTIMORE), H. W. NEWMAN (SAN FRANCISCO), J. DOUPE (WINNIPEG).

(From the Research Unit, National Hospital, Queen Square, London.)

It has been found that stimulation of the skin by alternating or faradic current causes secretion of sweat in the surrounding area. In the present paper this response is described together with some experiments carried out to determine its mechanism.

Methods.

The stimulating current was applied by a needle electrode which was guarded to within 1 mm. of its tip. This permitted adequate contact with a minimum of trauma to the skin. The indifferent electrode, a zinc pad moistened with saline, was strapped to the skin some distance from the area under observation. The current was derived from an audiometer circuit which allowed the regulation of frequency, amperage and voltage. Unless otherwise stated, the stimulating current was 0·25 to 0·5 milliampere at 50 cycles per second for one minute. Sweating was detected by the method of Minor (1929). After the selected area of skin had been cleansed with ether it was painted with a solution consisting of iodine 1·5 grm., oleum ricini 10 c.c. and absolute alcohol 90 c.c. When this had dried the area was lightly dusted with powdered starch. Sweat was easily recognized by the appearance of blue-black dots on the light-brown background. The majority of observations were made on the fore-arm of subjects in a moderately warm state. The subjects consisted of a group of five normal young adults and a group of ten patients with lesions of the nervous system. The site of the lesions will be described with the results obtained in these subjects.

Results.

General description.—Approximately 200 observations have been made on the volar surface of the forearm. The usual response consisted of sweating around the point of stimulation in an oval area approximately 3 by 5 cm. disposed longitudinally in the axis of the limb. The response

[1] Work done while Dr. Doupe held a Halley-Stewart Research Fellowship, Dr. Newman a Rockefeller Fellowship, and Dr. Wilkins a Fellowship of the American College of Physicians.

commonly extended slightly further in the distal direction, and its borders were irregular. Not infrequently a group of glands 8 or 10 cm. from the point of stimulation and generally situated distally were activated. There was, however, considerable variation in the area of the response obtained from stimulation of different points.

The sequence of events was as follows. After a latent period of ten to fifteen seconds from the beginning of stimulation, secretion, as shown by the appearance of discrete blue spots, began in the glands closest to the point of stimulation, and then spread to glands in the more outlying area. At the same time that those farthest away showed evidence of secretion some of the more central glands were still inactive. The intensity of the response in terms of the number of glands was greatest near the site of stimulation and not infrequently the blue spots coalesced. Sometimes the border was fairly sharp, while at other times it was vague, with the secreting glands separated widely at the periphery. The amount of sweat secreted by individual glands also appeared to be greater nearer the point of stimulation. In several instances after the cessation of the stimulus fresh spots appeared. When the duration of stimulation was prolonged to five minutes, few fresh spots appeared after the first minute, but the amount of sweat secreted increased with the duration of the stimulus.

The pilomotor response described by Lewis and Marvin (1927) appeared some two to five seconds before sweating was evident. While the areas involved were approximately the same size, the distribution of the goose flesh and secreting glands did not always coincide.

General conditions necessary for the production of the response.—The response was most easily elicited in subjects who were on the verge of sweating and when the skin was warm. It was, however, obtained even when the subject was so cold that he was shivering. In this instance the response was augmented in size and intensity by shining a warm light on the part under observation. This indicated the importance of the temperature of the skin, which was shown in another way. Two flat-bottomed test tubes 1 cm. in diameter were applied to the skin 1 cm. apart. One was filled with ice water and the other with water at 45° C. Stimulation at a point midway between the two tubes produced a response which was deficient under the cold tube and intensified under the hot.

Variation in different regions of the body.—The response on the forearm has been described above. Very rarely were points encountered which on stimulation gave rise to no sweating. Changing the position of the electrode by as little as 2 to 3 mm. was sufficient to enable a good response to be obtained. Observations on other parts of the body showed that the

degree of response was roughly parallel to the number of sweat glands present in the regions examined, as given by Kuno (1934 *a*). On the forehead near the mid-line the response was intense and fairly linear in a vertical direction. It did not cross the mid-line in three normal subjects and in three subjects with unilateral root section of the 5th sensory root. In the latter the sweat response did not spread from the anæsthetic area across to the normal side, nor in the reverse direction. More laterally on the forehead the response was sparse, as it was also on the anterior surface of the chest, the thigh and the calf. On the dorsum of the foot a moderate response was obtained, which was again disposed in the long axis of the member. On the chest an attempt was made to determine if the response crossed the mid-line. Stimulation at a point 1 cm. to the right of the mid-line produced sweating which extended 1 cm. to the other side. Owing to the small size of the response in this region it was not possible to obtain evidence sufficient to exclude the possibility of this spread to the other side being due to overlap across the mid-line.

It has been noticed that sweat appeared on the palms regardless of the site of the stimulus. This was interpreted as a response to the pain. When the stimulus was applied to a point on the palm the usual local response was not obtained; on the contrary the diffuse palmar sweating arising from the pain of the stimulus seemed to be locally inhibited.

The stimulus.—Various types of stimuli were used in an attempt to provoke the local sweat response. Injury to the skin by crushing and other forms of trauma caused no sweating, even though a well-marked flare developed. Intense heating by focusing the rays of a powerful lamp on a spot 2 to 3 mm. in diameter caused a slight production of moisture in the area heated, but no suggestion of a spreading response. Kuno (1934 *b*) in a similar experiment failed to obtain any evidence of a spreading response beyond the area locally heated. Stimulation with a constant direct current of 1 milliampere or with an alternating current of 25 milliamperes at frequencies above 10,000 cycles did not produce sweat. The optimum frequency for the production of the response was investigated by choosing a point on the fore-arm which on stimulation at 50 cycles gave a good response. To this point repeated stimulations at varying frequencies for one minute were applied and the results compared. The optimum frequency was found to lie between 10 and 30 cycles and the limits between 5 and 10,000 cycles.

Latent period.—The latent period before the appearance of sweat varied with the strength and frequency of the current. Using 0·25 milliampere at 50 cycles it ranged from ten to twenty seconds. That the stimulation had

produced some effect before this time was indicated by the following observation. In response to a current of 0·1 milliampere at 50 cycles sweat appeared at twenty-six seconds. The area was then reprepared and the same spot stimulated with the same current for periods of three seconds at one-minute intervals. Sweat appeared during the third period of stimulation. It was thus apparent that some change had occurred in the glands within three seconds of stimulation and that this state continued after the cessation of the stimulation. It was also found that prompt re-stimulation of a spot from which a good response had been obtained occasionally produced immediate sweating. It was not possible to demonstrate what portion of the apparent latent period was required for mere filling of the ducts of the glands.

Constancy of the response.—Maximal stimulation at one spot on repeated occasions produced responses of the same general configuration with the same glands participating. This was found by careful experimentation with a magnifying lens, the spots being related to lines drawn on the skin with Ziehl-Neelsen stain. Local heating of part of the area involved in the response during the stimulation increased the amount of sweat secreted but not the number of glands secreting in the part heated.

Area of overlap.—It was readily demonstrated by a series of stimulations at a number of points separated by 0·5 cm. that the areas of the different responses showed considerable overlapping. The borders of the response did not shift regularly with the change in site of the stimulus, but due to the wide variations in the size and shape of the response produced from different points no further conclusion could be drawn from this procedure. A more particular examination of the response of one gland was made with a magnifying glass. This showed that the same gland could be activated by stimuli applied at points 2 cm. apart, although very many of the glands which partook in the one response did not do so in the other, and the general configuration of the two responses was dissimilar.

Nervous pathways.—That the response was dependent on nervous connections was repeatedly shown in normal subjects by the absence of the response after laying down a novocain wheal at the site of the stimulus. A control injection of normal saline did not alter the response. Further evidence was obtained in a patient who had sustained trauma to the right brachial plexus seven months previously. There was complete wasting of the fore-arm muscles and complete loss of sensation in the segmental distribution C5 to D1. Stimulation in the anæsthetic area gave no response even though the part was artificially warmed. The possibility that the sweat glands in this region had become atrophied was excluded by the

widespread sweating induced by the intracutaneous injection of 0·1 c.c. of 5 per cent. mecholyl. Stimulation of the normal arm in this subject produced a marked response. An intact peripheral nervous system is thus a requisite for the production of the response. In two individuals who had undergone excision of the stellate ganglion some years previously no response was obtained in the arm deprived of its post-ganglionic sympathetic nerve fibres. It appeared, therefore, that an intact post-ganglionic sympathetic innervation was necessary. Two patients with section of the thoracic sympathetic trunk immediately below the stellate ganglion and two with lumbar sympathectomy had normal responses in the affected areas. That the operative procedures had been successful and that regeneration had not occurred in these cases was shown by the complete absence of sweating on the palms or soles in response to a painful stimulus. This simple test offered a very precise criterion for the determination of the continuity of the pre- and post-ganglionic sympathetic nerves. The results obtained in these subjects showed that the pre-ganglionic connections of the sympathetic fibres were unnecessary for the production of the local sweat response to faradic stimulation. It was then shown that the ganglion itself played no part by three experiments in which a cutaneous nerve was blocked with 2 per cent. novocain. It has been repeatedly shown that this procedure prevents sweating of central origin in the peripheral area of anæsthesia, yet in this area the local response was obtained with ease.

Attention was next given to the mode of spread of the response. The fact that repeated stimulations of one spot always activated the identical group of glands suggested that a nervous connection existed between the point of stimulation and the glands. This was confirmed in the following way. First, it was determined that an intradermal injection of normal saline in no way affected the response. Secondly, on fifteen occasions 0·1 c.c. of 2 per cent. novocain was injected intracutaneously to form a small wheal. Stimulation on top of the wheal caused no response. Stimulation slightly to either side of the wheal produced sweating in the usual area, except on the surface of the wheal and in a segment on the opposite side. The borders of the small region where sweating was absent were not strictly radial, but appeared to be more nearly parallel and separated by approximately the width of the wheal. This was true so long as the wheal had a diameter greater than 0·5 cm. A smaller wheal permitted the passage of the response around it. That even such small wheals were effective in blocking the nerves was indicated by the observation that stimulation in the zone of anæsthesia around and on top of the wheal produced

no response. Furthermore, it was found that the effect of a sweat-stimulating drug, mecholyl, which introduced intradermally rapidly diffuses and gives a wide area of sweat (Myerson *et al.*, 1937) was not altered by intradermal novocain, except that sweat did not appear on the wheal.

Using the rubber band technique of Lewis (1937) it was found that the nerves mediating the responses were relatively undisturbed by pressure. On three occasions a tense rubber band 10 mm. in width was placed across the volar surface of the fore-arm. It was found that stimulation to either side of the band caused sweat to appear on the other side. This phenomenon was still present after 30, 37 and 120 minutes, at which time there was well-marked analgesia in a tongue-shaped area extending 3 to 4 cm. distal to the band.

Incidental observations.—Stimulation to one side of an intradermal injection of 0·2 c.c. of 0·2 per cent. atropine inhibited sweating locally, but did not otherwise affect the spread of the response. A wheal produced by an injection of 0·05 per cent. prostigmin showed an augmented response on its surface after stimulation to one side of it.

Discussion.

It is recognized that electrical stimulation is an unnatural means of producing sweat and that this response may not occur physiologically in a normal subject. However, the activity of a sweat gland induced by this means has apparently the same peripheral mechanism as that brought about by normal innervation, for it is inhibited by atropine, augmented by prostigmin, and has the same relationship to the temperature of the skin (Kuno, 1934 *c*). That sweat glands themselves and not simply their smooth muscle fibres are stimulated by the faradic current is indicated by the observation that continued and increasing quantities of sweat could be produced by prolonged stimulation. The possibility that spread of current may directly stimulate the glands is ruled out by the observations that stimulation at certain points is ineffective, while a slight shift in the position of the electrode produces a good response, and that stimulation over very small wheals of novocain does not produce the response.

It has been shown that this local sweat response to faradic stimulation is dependent on the integrity of sympathetic fibres to the skin, but that it is independent of their ganglionic connections. It is possible that following stimulation locally a substance is produced which diffuses radially from the point of stimulation. It is apparent, however, that the diffusion of a sweat-producing substance would not explain the constancy of the response nor the blocking action of intradermal novocain on the spread of the

response. The length of the latent period does not require a process of diffusion; this is especially so as it has been shown that a stimulus has some effect on the glands within three seconds. All the evidence supports the view that the response is mediated by a branching axone system and thus resembles the pilomoter response described by Lewis and Marvin (1927). The fibres mediating the response lie in the skin, as the response is stopped by intradermal novocain. It may also be deduced that they are very small fibres from the fact that they are relatively immune to compression and have a low optimum frequency of stimulation.

The spread of the response is of some interest, as its analysis may give a clue to the arrangement and distribution of the terminal filaments of the sympathetic nerves. The fact that one gland may be stimulated from several different points might suggest that each individual gland has a multiple innervation. This is improbable because of the large number of nerve endings which would be required. Another explanation is the presence of a peripheral plexus or interlacing network of nerves. Such a plexus fails to explain why the response does not pass around a wheal of novocain.

Another possibility, better supported by the experimental evidence, is that not one but numerous interdigitating branched axone systems are being stimulated. It is suggested that the sympathetic fibres innervating sweat glands divide near their terminations into many fine filaments which radiate through the skin in all directions. Each such ramification may be called an axone system. These axone systems overlap each other to a very considerable extent, and at any given point in the skin many axones belonging to different systems are present. It is evident that an axone system which has its centre near the site of stimulation will be much more likely to supply a fibre passing this point than one which has its centre further away. This conception would fulfil the following requisites. Stimulation at a single point would activate the majority of the glands close to the site of stimulation. As the axone systems supplying the glands lying at the periphery of the response would not all be represented at the point of stimulation, only such as are there represented would respond. The glands at the periphery which did respond would usually do so later and less intensely than those near the stimulus, because the axone systems supplying them would be less likely to receive the full force of the stimulus than the axone systems whose fibres are concentrated at that point. Stimulation at one point on repeated occasions would give consistent responses. Stimulation at many different points along the one axone system would always cause a given gland to secrete. A very small wheal

of novocain would not entirely block the passage of impulses to the glands on the other side of it, while a larger wheal would do so. It would not matter to which side of the novocain the stimulus was applied. By the simple modification of making each axone system extend over a narrower and more elongated area the shape of the response on the forehead and foot would be explained. Inasmuch, therefore, as this theory fits all the observed facts it is suggested as a probable representation of the actual conditions present. If this be granted, it may be deduced that the diameter of an axone system is equal to the radius of the response. There must, however, be considerable variability in the length of the terminal radiating filaments to account for the outlying groups of glands which may be activated.

SUMMARY.

A local sweat response to faradic stimulation of the skin has been described.

It depends on a local axone reflex mediated by the post-ganglionic sympathetic fibres.

Many overlapping axone systems are involved.

The authors wish to express their gratitude to Professor J. Paterson Ross for making available the subjects on whom sympathectomy had been performed, and to Dr. E. Arnold Carmichael, under whose direction the work was carried out.

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DISSEMINATION OF A GLIOMA OF THE SPINAL CORD IN THE LEPTOMENINGES.[1]

BY KENNETH C. EDEN.

SINCE Ollivier (1837) first described the condition a number of cases of so-called "primary diffuse sarcomatosis of the cerebral and spinal meninges," have been described. The later discovery of neuroglial fibres in such new formations led Pels-Leusden (1898) to employ the term glio-sarcoma. When the difference between sarcoma of connective tissue derivation and glioma arising from the central nervous system became clear, this self-contradictory term was abandoned.

More recently, Bailey and Cushing (1925) were able to show that the mid-line cerebellar glioma, medulloblastoma, of children displayed a tendency to spread in the leptomeninges and was not uncommonly responsible for such dissemination.

Subsequently, Cairns and Russell (1931) and others reported examples of metastasis in the case of other varieties of glioma.

The present paper records and discusses a case of generalized lepto-meningeal dissemination, showing many of the features of primary meningeal sarcomatosis, arising from a glioma of the spinal cord.

The patient was a man aged 19, a hairdresser, admitted on August 28, 1936, to University College Hospital under the care of Dr. F. M. R. Walshe. Apart from appendicitis and mastoiditis in childhood he had enjoyed good health until the onset of the symptoms now to be described. Seven weeks before admission to hospital he began to notice a sensation of "pins and needles," first in the right, and within a few days in the left, leg. This was accompanied by numbness and quickly spread up to the thighs. Both legs then began to grow weak, the right before the left, and within a few days both were severely paralysed, movements at the hips being less impaired. There was neither pain nor disturbance of sphincter control.

A course of massage and electrical treatment at another hospital effected a temporary improvement, so he thought, but the weakness soon increased again.

On examination he proved to be thin and pale, in no pain and with a normal temperature. He was intelligent and co-operative. The mouth, thoracic and abdominal viscera appeared normal. There was an old perforation of the right ear-drum with some deafness of middle-ear type. The fundi and cranial nerves were normal. There was no neck rigidity.

[1] From the Surgical Unit, University College Hospital.

The legs were paralysed, except for feeble movement at the hips. The abdominal muscles were normal.

All forms of sensation were severely impaired below the middle of the thighs anteriorly, and below the lumbosacral junction posteriorly. Below the knees postural and vibration sensibility was absent.

The arm-jerks were normal, but the knee and ankle jerks abolished on both sides. The plantar responses were both of extensor type, the abdominal reflexes and the anal reflex were normal.

Kernig's sign was absent.

Lumbar puncture revealed an incomplete block, with an initial pressure of 250 mm. water, and a slow rise and delayed fall on jugular compression. The fluid was clear and yellow in colour. It contained two cells per c.mm., an increased globulin content, chlorides 0·73%, sterile on culture. In the blood the hæmoglobin content was 106%, colour-index, 0·92, R.B.C.s 5,850,000, W.B.C.s 6,400, and polymorphonuclear cells 64%. The Wassermann reaction was negative in both blood and cerebrospinal fluid. A radiogram of the spine revealed no abnormality.

On September 29, cisternal puncture, and lipiodol (2 c.mm.) injection were performed. The theca punctured easily, but there was some difficulty in introducing the lipiodol, and during the procedure the patient collapsed and vomited several times. A radiogram showed that only a few drops of lipiodol had entered the theca, the rest having passed extrathecally.

Clinical Course.

During the night of October 10 he suddenly complained of pins and needles in both arms, developed complete dysarthria and vomited repeatedly. A few hours later he was able to say "Yes" and "No," but otherwise his speech was unintelligible. Next day the speech had improved, but there was loss of power of protrusion of the tongue, slight weakness of the right arm and leg and the lower right face. Shortly afterwards he developed severe headaches, vomiting, and diplopia, with a left external rectus weakness. This all cleared up during the next week, but he then began to have difficulty in micturition and developed retention of urine. The urine contained pus and red cells and a culture grew *Bacillus coli*. From then onwards he was catheterized twice daily with regular bladder washouts of 2% mandelic acid.

On October 16 he was transferred to the Surgical Unit Ward. The squint, facial palsy and weakness of the right arm had disappeared completely. The paralysis and anæsthesia of the legs were unchanged but spasticity was becoming marked and flexor spasms could be elicited readily by pin-prick on either leg. There was a subjective sensation of "pins and needles" in the buttocks and front of the thighs, but no area of hyperæsthesia could be found.

Laminectomy was performed by Mr. Wilfrid Trotter under general ether anæsthesia on November 24. The spines and laminæ of the 11th and 12th dorsal and 1st and 2nd lumbar vertebræ were removed. The dura appeared to bulge under tension and was opened. The arachnoid was thickened and the cauda equina matted. No definite gelatinous exudate was observed at operation. The lower part of the lumbar enlargement and conus medullaris were uniformly expanded and were considered to be the site of an intramedullary tumour. No attempt was made to remove it, the dura was left open and the wound closed.

At the end of a week sensation in both legs had improved very slightly and firm

pressure was just appreciated after a delay. He then began to complain of failing vision at this time and examination revealed two dioptres of papillœdema in the right eye and a distinct temporal pallor of the left disc. His hearing, which had always been poor, also deteriorated and a moderate degree of nerve deafness was

FIG. 1.

FIG. 2.

FIG. 1.—Base of the brain, showing tumour lying in basal cisterns and surrounding infundibulum, and spread over brain-stem, cerebellum and temporal lobe.

FIG. 2.—Dorsal aspect of lower thoracic of lumbar and sacral regions of cord, showing the diffuse leptomeningeal infiltration by tumour.

discovered in the left ear in addition to the chronic middle-ear deafness on the right side associated with an old perforation. He had three large bed sores on the buttocks which were proving very resistant to treatment. Early in December he became incontinent of urine and fæces, which persisted from then until his death on January 26, 1937. He became gradually more drowsy and incoherent, with a

great deal of vomiting, confused articulation and wandering of the mind and there were two attacks of generalized convulsions lasting a few moments and accompanied by a loss of consciousness, neck retraction and twitching of all the limbs.

AUTOPSY EXAMINATION PERFORMED BY PROFESSOR G. R. CAMERON ON JANUARY 27, 1937.

The subject was a pale, emaciated man with a healed laminectomy scar in the lumbar region and three large unhealed bed sores, one over the sacrum and two on the buttocks.

Brain.—The dura mater was everywhere intact and normal. The arachnoid was tensely distended by a gelatinous, pinkish-grey exudate. This was least marked over the cerebral hemispheres, but very dense at the base of the brain. The infundibulum and optic chiasma were partially buried in a thick, gelatinous mass

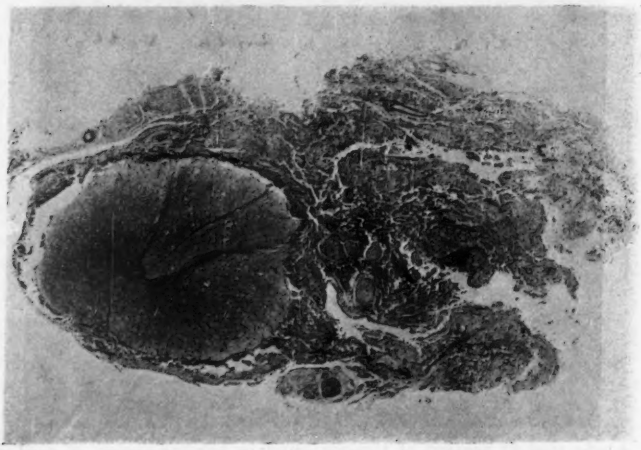

FIG. 3.—Cross section of thoracic region of cord, showing a cuff of tumour. (× 6. van Gieson stain.)

of tumour which filled the interpeduncular space and largely obscured the circle of Willis and the origins of the cranial nerves (fig. 1). The pons and medulla were surrounded by growth. A thin film of tumour spread out in the leptomeninges over the surface of the cerebellum and along the sulci of the temporal lobes. The ventricles were moderately and uniformly dilated but no definite tumour masses were detected. The exudate could be traced as a thin layer along the floor of the 4th and 3rd ventricles into the right lateral ventricle but not into the left. Careful sections of the cerebellum revealed no trace of a primary tumour and a similar investigation of the whole of the remainder of the brain was negative.

Spinal cord.—The dura was uninvaded but tensely distended by the tumour. The pia-arachnoid throughout the length of the cord was replaced by gelatinous tumour (fig. 2). This was most marked on the posterior aspect and the right side and continuous with the infiltration at the base of the brain. In the dorsal

region the cord was displaced to the left by the dense accumulation on the right side (fig. 3). The origins of the nerve roots were partially hidden and surrounded by a cuff of tumour as they entered their dural sheaths. In the lower part of the lumbar enlargement the outline of the cord, which everywhere else was quite distinct, was indefinite and the cord was replaced by an irregular pinkish-grey tumour continuous with the growth in the leptomeninges. The cauda equina was densely matted and studded with nodules of soft irregular growth.

Other organs.—The tongue, mouth, pharynx, tonsils, salivary glands and œsophagus were all normal ; the stomach contained a little mucus and brownish fluid and showed a few scattered submucous petechiæ. The intestinal tract was normal. The heart and aorta showed no abnormality. The lungs were healthy except for a few old pleural adhesions and the bronchi contained only a little mucus. The liver,

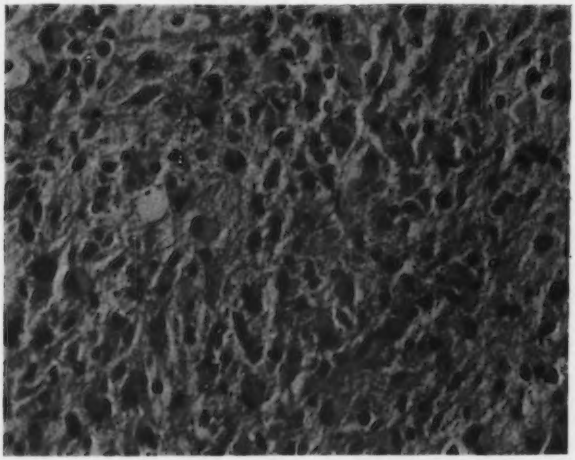

FIG. 4.—Section of portion of tumour lying in lumbar region of cord, showing general cellular structure. (× 320. Hæmatoxylineosin.)

gall-bladder and spleen were healthy, the bladder contracted and congested with signs of acute inflammation and hæmorrhages, most marked over the trigone. The prostate, vesiculæ seminalis and testicles were normal. The suprarenal glands were of average size and showed no tumour deposits. The thyroid was pale yellow and of normal size. Both eyes and orbits showed no growth.

Microscopic appearances.—Sections of various parts of the cord and brain were stained with hæmatoxylin and eosin, van Gieson, Mallory's connective tissue stain, Mallory's phosphotungstic acid hæmatoxylin, Perdrau's silver impregnation for reticulum and Wilder's silver impregnation for neuroglial cells and nerve cells.

Sections through the lower lumbar region of the cord showed invasion throughout by cellular tumour (fig. 4). In places recognizable spinal cord substance could be detected although the delineation of grey and white matter was completely destroyed. Elsewhere the mass consisted of a densely cellular tumour continuous with an infiltration of the leptomeninges. The vasculature was very rich, consisting mainly

of numerous branching arterioles with fairly well-formed walls. In places they were somewhat varicose. There was no endothelial proliferation or hyalinization of the walls and no areas of necrosis were present in the tumour. By Perdrau's method the blood-vessels showed up clearly with a small amount of connective tissue around them and only a little reticulum scattered in between. In sections stained by hæmatoxylin and eosin the cells showed a great variation in size and configuration. The commonest type was one with a round or oval nucleus deeply hyperchromatic, with dense chromatin particles scattered throughout the nucleus. In some cells the chromatin was so dense that no structure could be made out in the nucleus. The cytoplasm was irregular and poorly stained. Many of the cells resembled large and small astrocytes with typical oval nuclei of medium size and scattered chromatin and swollen, badly-stained, branching cytoplasm, the nucleus very often being pushed to one side. In addition there were a considerable number

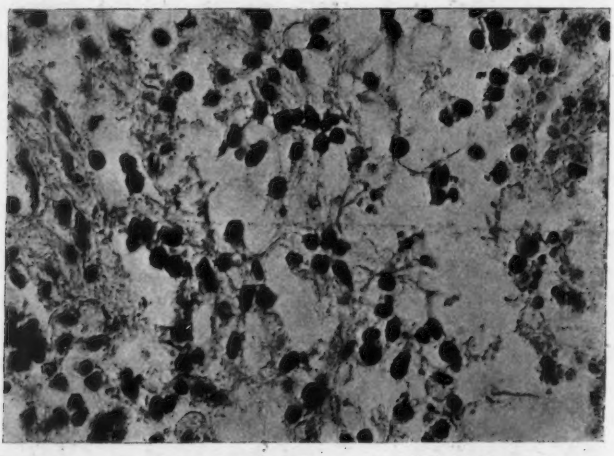

FIG. 5.—Tumour showing neuroglial fibres. (× 500. Mallory's Leptomeningeal phosphotungstic acid hæmatoxylin.)

of cells resembling spongioblasts. The nuclei of these cells were very large and hyperchromatic, often multiple or bilobed with cytoplasm forming one or two branching processes.

Here and there in the remnants of cord substance a few nerve cells could be picked out, all in various stages of degeneration and many with swollen and hydropic cytoplasm. In preparations stained with phosphotungstic acid hæmatoxylin, neuroglial fibres were fairly plentiful, forming a network throughout the tumour (fig. 5). One or two centrosomes could also be made out. Occasional mitotic figures were present but they were not very pronounced. With silver impregnation preparations the majority of cells were large and irregular with one or more branching processes, some of them frayed at the ends. Only one or two sucker processes were found. Large and small astrocytes, unipolar and bipolar spongioblasts were all readily identifiable.

Elsewhere in the cord the leptomeninges were densely packed by cellular

infiltration invading the sulci and surrounding the blood-vessels and nerves but not extending into the substance of the cord. A thin layer was also present over the entire cortex invading the cerebral sulci and Virchow-Robin spaces but not spreading into the subcortical white matter. With van Gieson preparations a well-marked fibroblastic reaction was shown to be present, mostly adjacent to the cord and around the blood-vessels and nerves but also scattered irregularly throughout the infiltrating tumour. Among the bundles of collagen fibres the more elongated spindle-shaped vesicular nuclei of the connective tissue cells were readily distinguishable from the invading tumour cells. With Perdrau's method the reticulum was seen to be scattered irregularly in a radial manner between the blood-vessels without any concentric ring formation but was a little more plentiful adjacent to the blood-vessels than elsewhere (fig. 6). The striking characteristic of the

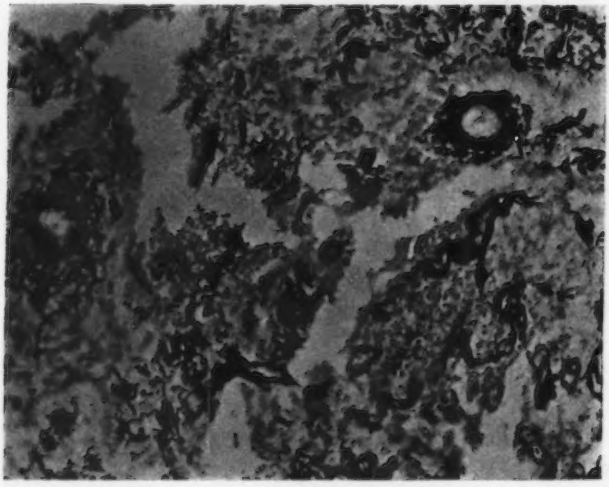

FIG. 6.—Leptomeningeal tumour, showing fibrous tissue and reticulum. (× 120. Perdrau's method.)

tumour infiltrating the leptomeninges as compared with the tumour in the cord was the comparative uniformity of the cells. In preparations stained with hæmatoxylin and eosin there was a great preponderance of the smaller cell type with a few spongioblasts scattered throughout. Mitoses were rather few. Phosphotungstic acid hæmatoxylin preparations showed a network of neuroglial fibrils. In most of the cells few processes were distinguishable with the silver impregnation method but here and there were small astrocytes and spongioblasts. The large astrocytes were much more infrequent here.

The multicellular character of this tumour makes it difficult to place it in any of the usually accepted classifications of gliomas. Its cellular character suggests its inclusion amongst the glioblastoma multiforme group, but the lack of degenerative and characteristic changes in blood-vessels seems rather to weigh against this. It is therefore best regarded as a mixed-cell glioma of uncertain nature.

Discussion.

The capacity of gliomas to metastasize by way of the cerebrospinal fluid was not recognized until comparatively recently. Such metastases had not been recorded elsewhere in the body and the glioma was regarded as a tumour of purely local invasive character.

Recorded examples of diffuse formation of tumour in the leptomeninges had therefore been looked upon as a primary diffuse sarcomatosis. Later, with the improvement of methods of staining, neuroglial fibres were detected in such tissue.

Ford and Firor (1924) published a case of gliomatosis of the leptomeninges and listed nine other cases from the literature. It was only when Bailey and Cushing described the clinical and pathological features of the mid-line cerebellar medulloblastoma in children with dissemination in the leptomeninges that it began to be possible to classify these tumours. They were able to show that a large number of the cases described in the literature as diffuse tumours of unknown origin, were in reality examples of this condition. These included the original case of Ollivier, several of the cases discussed by Ford and Firor, and many others. Since then further examples of dissemination by other types of glioma have been recorded, although no other tumour has been shown to manifest the same readiness to spread in the leptomeninges as the cerebellar medulloblastoma. Cairns and Russell's group of cases showing intracranial and spinal metastases in gliomas included in addition to further examples of cerebellar medulloblastomas, instances of neuro-epithelioma of the retina, glioblastoma multiforme, astrocytoma and ependymoma. They concluded from their observations on twenty-one consecutive full autopsies in cases of glioma, in which eight showed spinal metastases, that the frequency of this process is much greater than had been supposed.

The instances of dissemination of spinal tumours are very few in the literature. Frazier (1918) stated that pure intramedullary spinal tumours are limited to the cord itself and never invade the meninges. Kernohan (1932) was only able to give one example and that was of an oligodendroglioma of the cord which was exposed at operation and decompressed by a vertical posterior incision into the cord. At autopsy the tumour was found to have spread upwards and downwards for a short distance in the leptomeninges with a well-marked fibroblastic reaction. Elsberg (1925) described no examples of dissemination of tumours of the cord, but emphasized their tendency to extrude themselves and grow out of the cord substance. Grund (1906) recorded a case of a large intramedullary tumour of the cervical spinal cord with infiltration of the adjacent leptomeninges and Rutimeyer

(1930) described an intramedullary tumour in the lower part of the cord which had spread up as far as the cervical cord. Professor Forster has very kindly allowed me to refer to an instance in his extensive series of spinal tumours which he will discuss in his book on tumours of the brain and spinal cord. This was described as a medulloblastoma of the lumbar cord in a young woman aged 29, which spread throughout the subarachnoid space of the spinal cord, base and convexities of the brain. In the case recorded by Pels-Leusden of compression of the lumbar cord by a tumour mass with diffuse dissemination in the leptomeninges which he described as a gliosarcoma, there was a mass of growth in the left lateral ventricle which it is impossible to exclude as the primary tumour.

There remain a number of cases in which after detailed examination no primary tumour has been discovered in the central nervous system. According to Willis (1934) some of these cases are due to carinosis. In his opinion the case of diffuse tumour spread described by Olivecrona (1914) is an example of this condition. Nodules of growth were found in several of the viscera, one of which might have been the primary growth. In addition some of the diffuse leptomeningeal growths have been pigmented and small unrecognized melanotic growths of the skin or the eyes may have been overlooked. In other cases in which these primary sources have been eliminated it seems possible that the growth may have originated in areas of pigmentation in the central nervous system. Masson (1926) believes that the presence of pigment is indicative of an ectodermal rather than a mesodermal origin and this is significant in view of Harvey and Burr's (1926) conclusions that the meninges are really of ectodermal origin.

The existence of true diffuse primary sarcomatosis of the leptomeninges is somewhat doubtful. Bailey (1929), however, still believes that it exists as a definite pathological entity with characteristic features. He points out that there are cases of diffuse leptomeningeal growth in which no primary tumour has been found and that in contradistinction to the medulloblastomas of children they occur in adult subjects. They originate by a sarcomatous transformation of the perivascular sheaths—"the peritheliomas"—which may be distinguished from gliomatous invasion of these sheaths by the intact pia-glial membrane in the latter. The cells in these tumours, he says, tend to be arranged in cuffs around the blood-vessels, often several cells thick and the reticulum is plentiful and distributed in concentric rings around the blood-vessels. The infiltrating gliomas may contain reticulum, but it is more scanty and irregularly arranged in a radial manner between the vessels. Moreover the nuclei of the connective tissue in the leptomeningeal gliomas may be clearly picked out from the glial cells, whereas in the peritheliomas only one type of cell is present.

The possibilities which were considered in the case under discussion were that it was a case of primary sarcomatosis of the meninges, a disseminated cerebral glioma invading the lumbar cord, or a spinal glioma with leptomeningeal spread. The latter explanation was held to be the only tenable one in view of the evidence. Clinically the paraplegia marked the onset of symptoms and predominated throughout in spite of the subsequent scattered signs elsewhere in the nervous system. At operation the lower lumbar and sacral cord was seen to be enlarged and thought to be the seat of an intramedullary tumour, but no disseminated tumour was then observed. The autopsy revealed no primary tumour in spite of careful search in the nervous system or elsewhere, but a mass of gliomatous tissue was found replacing the lower part of the cord. The microscopic examination revealed the fact that the cells invading the leptomeninges were glial in origin and distinct from the connective tissue cells which lay in relation to the fibroblastic reaction. The reticulum was scanty and irregular in distribution. The difference in the cellular structure of the primary tumour in the cord and the leptomeningeal infiltration was thought to depend on the nature of the tissue invaded, the fibroblastic reaction and the predominance of the smaller cell type occurring in the meninges and the densely cellular structure with large numbers of spongioblasts characterizing the primary tumour.

It is not clear why certain gliomas show a marked tendency to spread in this manner and others do so only rarely. The most important single factor would seem to be the nature and degree of malignancy of the tumour. The position of the tumour in close relationship to the ventricles or cisterns naturally is of importance. However, very many tumours impinge on the subarachnoid space without apparently giving rise to any metastases, although Cairns and Russell's observations indicate that the frequency may be greater than is thought. Operative interference has also been thought to play a part by the scattering of cellular emboli in the cerebrospinal fluid and the opening of deep-seated tumours to the subarachnoid space. The natural tendency of the cerebellar medulloblastomas to disseminate is such that the role of operative interference in these cases is very difficult to assess. Kernohan's case of oligodendroglioma of the cord which was incised with subsequent leptomeningeal infiltration, would seem to suggest that the exposure of the tumour substance to the cerebrospinal fluid determined the dissemination. In the case described in this paper, however, the cord was not incised and it is probable that dissemination had already begun before the operation.

Examination of the recorded cases indicates two types of metastases in gliomas. In a variety of tumours scattered nodules have been observed

on the posterior aspect of the cord, at the base of the brain and in the floors of the ventricles. The supposition is that cellular emboli are thrown off from the tumour into the cerebrospinal fluid, are carried into the perivascular spaces and settle in the dependent part under the influence of gravity. Some of these emboli continue to grow and form secondary nodules of growth in the leptomeninges. The other type of spread is an apparently continuous permeation of the tumour throughout the leptomeninges. It is doubtful, however, if this process can be compared with lymphatic permeation. Gravity seems to play an important part here, too, and it is probable that in reality the same mechanism is involved but on a much larger scale than in the formation of nodular metastases. In the case described although there was a thin continuous layer of infiltrated tumour throughout the leptomeninges, the main accumulation was in the dependent parts. The patient lay throughout his illness on his back and right side and the tumour was found distributed most densely on the posterior and right sides of the cord, the base of the brain and in the right lateral ventricle, but not in the left.

The clinical picture of leptomeningeal dissemination of tumours is in no sense clear cut. Ford and Firor attempted to classify the cases into definite clinical types, but were confused by the various types of cases included. It is clear that the signs of dissemination may be superimposed on those of the primary tumour, as in the case described, or the primary tumour may pass entirely unnoticed. On the other hand a distinct interval may be present before dissemination is manifest, as occurred in a case of cerebellar medulloblastoma treated at this hospital by a posterior fossa decompression and X-ray therapy to the brain. All the signs of a tumour of the posterior fossa cleared up rapidly and the girl was able to get about quite normally for three months, after which she developed a paraplegia and died of generalized tumour dissemination. Winckelman and Eckel (1936) described a case in which the primary tumour of the cerebellum was actually removed and the patient was free from symptoms for two years before the onset of spinal invasion.

The variability of the clinical course with periods of exacerbation and remission which was manifested by the case described is very characteristic and has been noted by many writers. The cisternal puncture with alteration of the intracranial pressure disturbed the patient profoundly and it is probable that the difficulty in introducing any lipiodol inside the theca was due to the presence of tumour at that time in the leptomeninges. It is very difficult to understand why the isolated palsies which developed some days later should have cleared up completely. The complete absence of root pains is also a well-established characteristic, and was thought by Winckelman

and Eckel to be due to the soft nature of the infiltrating tumour. It is remarkable that although the leptomeninges were infiltrated throughout with tumour, the only permanent signs until very late were those of the primary cord tumour. This must be attributed to the absence of invasion of the nervous system except in the lumbar cord. The signs of raised intracranial pressure only developed to a severe degree in the last few weeks of his illness when the subarachnoid space was presumably dammed up. Meningeal signs were very inconspicuous throughout, although they might reasonably have been expected to predominate. The analysis of the cerebrospinal fluid should be of crucial importance in the diagnosis. It is unfortunate that the possibility of diffuse spread was not entertained in this case. Since Forster (1930) has shown that by a careful analysis of centrifuged cerebrospinal fluid in cases of cerebral and spinal gliomas, using special staining methods, it is possible to identify the characteristic tumour cells in a considerable proportion of cases, it should certainly be possible to detect the cells in large numbers in these cases of diffuse dissemination and in any suspected case it is most important to look for the cells.

Once the diagnosis is established the only rational treatment is deep X-ray therapy to the central nervous system, in view of the extreme sensitivity to irradiation of such tumours as the cerebellar medulloblastoma. Our experience in this hospital of a case of cerebellar medulloblastoma with irradiation of the primary tumour which was followed a few months later by spinal subarachnoid invasion, emphasizes the importance of irradiating all parts of the nervous system.

I am indebted to Mr. Wilfred Trotter and Dr. F. M. R. Walshe for permission to review this case, and to Professor G. R. Cameron, Dr. J. G. Greenfield and Dr. L. E. Glynn, for their help in studying the pathology, and to Professor O. Foerster for his kind permission to refer to his case.

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FIBRILLATION AND FASCICULATION IN VOLUNTARY MUSCLE [1]

BY D. DENNY-BROWN AND J. B. PENNYBACKER.

INVOLUNTARY fibrillary twitching of muscle is a phenomenon observed frequently in the course of clinical examination of patients suffering from nervous disorders. It is apparent to the naked eye that what is commonly called "fibrillation" in amyotrophic lateral sclerosis, for example, differs in type from muscle to muscle, and from time to time in the same patient. Of these differing varieties there is little mention in the literature, nor of their relationship to other kinds of involuntary twitching in muscle.

The following study is of myographic and electromyographic records of these various forms of involuntary twitching of muscle fibres.

(1) METHOD OF INVESTIGATION.

The twitching of the muscle has been recorded by concurrent records of the mechanical twitch and the electrical action current of the fibres concerned. The electrical action current has been recorded by inserting a hypodermic needle through the skin into the substance of the muscle being investigated, a superficial portion of the muscle fibre being selected for the purpose. The second electrode in the form of a thin copper wire insulated with cotton winding soaked in celloidin, with silvered perforation at its end, is inserted through the needle just to protrude through its end. Thus the tip of the wire core forms one electrode among the muscle fibres, separated by 1 to 2 mm. from the nearest part of the needle, which forms the other electrode. The wire and the hypodermic needle are connected to the input side of a four stage amplifier leading to a Matthews Oscillograph, of which the galvanometer mirror reflects a beam of light on a strip of moving bromide paper. Over the region where the tip of the hypodermic needle lies in the muscle a small cork button or pyramid is stuck to the skin by collodion. Over the button is a balloon lightly inflated with air, and held by adhesive

[1] This investigation was made in 1934-35 during the tenure of a Halley Stewart Fellowship by one of us (D.D-B.) in the Research Unit, National Hospital, Queen Square, London.

plaster to the body wall or to a metal guard clamped round the limb. Any mechanical movement of the piece of muscle concerned moves the cork, and produces a fluctuation in the air pressure in the balloon which is transmitted by a short length of pressure tubing to a manometer with mirror diaphragm. The movements of the manometer mirror are recorded by a beam of light which is reflected to the same strip of moving paper as records the action currents. The latency of the mechanical system used was 0·004 sec., i.e. the mechanical record lags behind the electrical record by this time interval. In the animal experiments fibrillation was recorded by a very small steel mirror directly applied to the muscular surface.

It cannot be too strongly emphasized that mechanical records made in this manner must be controlled carefully by visual observation of the surface of the muscle.

(2) Interpretation of Observations on Muscular Function.

Inasmuch as it is desired to discuss the relationship of different forms of involuntary twitching to the functional structure of muscle, it is desirable here to outline some anatomical and physiological facts relating to muscle. The unit structure of a muscle is a muscle fibre, a structure which has a diameter in man of from 0·01 to 0·10 mm., and in most muscles a length of 3 to 5 cm. In some exceptional muscles such as sartorius or platysma the length of the fibre may be as great as 12 cm. (Felix, 1887). Muscle fibres in skeletal muscle are independent structures with separate existence, and without syncitial interconnection, as can be demonstrated by teasing methods (Felix, 1887, Denny-Brown, 1929a). They can contract independently (Pratt and Eisenberger, 1919, Gelfan and Bishop, 1932).

Fibres are grouped in natural bundles called fasciculi, each containing many hundreds of parallel muscle fibres in a coarsely fasciculated muscle, such as gluteus maximus, or smaller bundles with less defined edges in pennate muscles such as the extensors of the wrist or the interossei. While a muscle fibre therefore is of a thinness which can just be detected by the naked eye, the fasciculus is a structure of some 2 to 10 mm. in diameter. The functional significance of the fasciculus appears to be its vascular arrangement, with terminal artery and independent veins. That it is not nervous is shown by the common pathological observation that, as a result of lesions affecting only a certain number of fibres in the motor nerve, a portion of a fasciculus may suffer extreme degeneration and the remainder appear healthy (Durante, 1902, Wohlfart, 1935).

Though physiologists have come to regard the muscle fibres as each having dependence upon one nerve fibre, and each motor nerve fibre serving in this way a number of muscle fibres, it has from time to time been asserted that muscle fibres derive motor supply from a plexus to which the total of the motor nerve fibres contribute (Wilkinson, 1931). Modern treatises on anatomy, histology or physiology give the reader no guidance, except to indicate that it has been asserted that muscle fibres receive more than one end plate. It is necessary, therefore, to present as briefly as possible the evidence for the first view, which appears to us to be well founded. The point is of importance to the understanding of the electromyogram as well as of the atrophy of muscle.

Each ordinary muscle fibre in a limb muscle receives one motor end plate. That this is the only end plate can readily be seen in cutaneous muscles or sartorius in the frog as studied by Krause (1869), Kuhne (1884, 1886), Kulchitsky (1924) and others, and with methylene blue staining their finding is readily verified. This arrangement of one motor ending to each muscle fibre has been found also in the silver impregnation staining of limb muscles of the developing mammal (Tello, 1917, 1922) and in sartorius, soleus, tibialis anticus, of the young cat as studied by one of us (D. D.-B.). The exceptions to the rule are the intrafusal muscle fibres of the muscle spindles (Agduhr, 1919), and some very long fibres in pleurisegmental cutaneous muscles such as the panniculus of the hedgehog (Garven, 1925). In the muscles of the tongue several nerve endings may commonly arise from a network of intercommunicating nerve fibres (Boeke, 1911, 1932), but it remains to be demonstrated that this arrangement is other than a persistence of the embryonic neurofibrillar network of a single motor neurone innervating a bundle of contiguous muscle fibres (Tello, 1922). Occasionally very long fibres are found with two end plates in the limb muscle of the frog (Krause, 1869), but these are exceptional and moreover it has not been demonstrated conclusively that the endings seen are not branches of the same parent nerve fibre.

The contraction of the same fibres in flexor communis digitorum in the pig by stimulation of the ulnar or the median nerve by Agduhr (1919), and the radicular innervation of all or nearly all this muscle by both 8th cervical and 1st thoracic nerve roots in this muscle in the rabbit by Lederer and Lemberger (1907) require further investigation, for the phenomenon does not appear compatible with common observation in clinical disorders of this muscle in man. Methods of recording contraction in which the muscle is permitted to shorten are not adequate to decide the point. (See discussion by Fulton, 1926, Chap. VI).

Agduhr (1916, 1919) has described double, and sometimes triple, innervation of muscle fibres of the flexor digitorum sublimis in animals by selective degeneration of the 8th cervical and 1st thoracic nerve roots. The three end plates he pictures are shown lying close together in different stages of degeneration. It is quite unknown for a normal muscle fibre to receive three end plates close together. In paraffin sections by the Bielchowsky method it is notoriously difficult to distinguish one muscle fibre from another just underneath it. For this reason Agduhr's findings cannot be accepted as indicating a general principle until confirmed by other, preferably teasing, methods.

Degeneration of muscle fasciculi following partial section of a motor nerve or nerve-root is partial ; thus groups of muscle fibres degenerate upon section of particular nerve fibres. There are no transitional forms of degeneration, so that muscle fibres do not depend, partially upon some nerve fibres partially upon others, but each upon its own particular motor nerve fibre. A classical example cited in opposition to this general principle is that of the crico-thyroid muscle which is stated by Exner (1885) and Livon (1891) not to degenerate when either one of its component nerve supplies, superior laryngeal, and laryngeal plexus, is sectioned. Exner states that the muscle degenerates if both nerves are sectioned. These observations are so directly at variance with the effect of stimulating the two nerves (Lederer and Lemberger, 1907), and the physiological and pathological findings quoted above, that its repetition with modern methods is highly desirable. Some muscles such as the external anal sphincter (Arloing and Chantre, 1898) are resistant to paralytic atrophy. The degeneration of muscle depends not at all upon sensory nerve fibres, nor is it delayed by their integrity.

Of the two or more nerve roots supplying a muscle, stimulation of one causes a contraction of a different part from that contracted by another (Gad, 1882, Sherrington, 1892, de Boer, 1925-26, Van Rijnberk, 1911) and fatigue of one group of fibres little affects the contraction from the other (Gad, Fulton, 1926, Van Rijnberk, 1929). When one group is already thrown into a fused contraction-tetanus by rapidly repeated stimulation, the other can be made to twitch in more isolated manner (Samojloff and Wassiljewa, 1925), the veratrin contracture of one group can be fatigued without that of the other (de Boer), and lastly the mechanical thermal and electrical effects of isometric contraction each of two such groups of motor fibres to a muscle can be summed almost exactly by combined stimulation of both motor roots together (Samojloff, 1924, Samojloff and Wassiljewa, 1925, Fulton, 1926).

From all these different points of view it may be concluded that each muscle fibre depends upon one nerve fibre, and therefore one motor anterior horn cell. Since the motor nerve to a muscle contains many fewer motor-nerve fibres than there are muscle fibres, and nerve fibres can be observed in stained preparations to branch in their course in muscle and supply many muscle fibres, it follows that one motor-nerve fibre supplies a whole and particular group of muscle fibres. This group is found by calculation (Clark, 1930) to average for instance some 150 muscle fibres for soleus in the cat (total 30,000 fibres) and in contraction to be responsible for only 10 gr. of maximal tension (Eccles and Sherrington, 1930). This motor-nerve fibre, its parent anterior horn cell, and its dependent group of muscle fibres have been termed the "motor unit" (Liddell and Sherrington, 1925, Sherrington, 1929, 1931, Eccles and Sherrington, 1930). Such a group can be observed to contract alone in an all-or-none manner in response to excitation of its motor nerve fibre (Pratt and Eisenberger, 1919, Pratt, 1925).

The action currents of a single motor unit in mammalian muscle have been recognized to have each a particular shape, and the discharge of a motor unit can be recognized in the electromyogram by the repetition of a regular shape of action current in series, producing a contraction tension of some ten grams only (Denny-Brown, 1929*b*, fig. 16). This demonstration of the function of a single motor unit was further amplified by Eccles and Sherrington (1930). The electromyographic appearance of the rhythmical electrical discharge has since become well recognized (Adrian and Bronk, 1929, Eccles and Hoff, 1932, and in human muscle by Smith, 1934, Lindsley, 1935-6). The diphasic variation which constitutes the action current of a group of muscle fibres alters in shape according to the disposition of the fibres in relation to the two points of the electrodes which sample the electrical change. The more truly the fibres lie across the two electrodes the more the electrical fluctuation approaches a simple diphasic variation. The closer to the electrode the larger the electrical change that is sampled. Thus each group of muscle fibres belonging to one motor unit lies in a particular position in relation to the points of a needle or other electrode inserted into the muscle, and a wave of contraction in them has a particular shape of electrical action current.

(3) The Fine Fibrillation of a Muscle Completely Deprived of its Nerve Supply.

Denervated mammalian muscle has long been known to exhibit a fine tremor of its surface. (Schiff, 1851, Langley, 1915-16*c*, Langley and Kato,

1914-15). Usually the tremor is so slight in degree that it is well seen only when the bared surface of the muscle is observed in reflected light. The surface of the muscle is observed to be rippled by a restless agitation without either apparent rhythm or obvious centre of activity. The whole muscle is involved in a confusion of very small twitches. Such fibrillation is related in some way to the wasting following denervation. In the frog, where denervated muscle wastes only very slowly, fibrillation does not occur. (Langley, 1915-16*c*). This phenomenon is most easily observed in man in the tongue when that organ is subject to paralytic atrophy, for here the superficial situation of muscle fibres and thinness of covering facilitate its observation. Where the skin and subcutaneous tissue are thin it can be observed in other skeletal muscles, particularly as a result of damage to peripheral nerves or degeneration of motor anterior horn cells as in poliomyelitis or syringomyelia.

The faint, confused agitation of the surface of the muscle is accompanied by a very fine rapid electrical fluctuation of which a characteristic instance is shown in fig. 1, taken from the mylohyoid muscle of a patient suffering from syringomyelia, with wasting and fibrillation of one half of the tongue and hyoid muscles. These action currents are much smaller than those accompanying motor nervous activity (cf. fig. 11 at the same amplification) and are of such size that they may be each due to the electrical variation of a single muscle fibre.

We have sought to examine this phenomenon further by experimental means by sectioning the sciatic nerve in cats under general anæsthesia, and examining the calf muscles at different periods after the nerve section. For this purpose the animal was decerebrated under deep anæsthesia, after the lapse of an appropriate time interval. The anæsthesia was then allowed to pass off[1] and two hours later the muscle concerned was exposed by skin incision, observed by reflected light, and the electrical record of its action currents made. Langley and Kato (1914-15) have established the onset of fibrillation in denervated muscle of the cat on the fifth day after nerve section and we have confirmed this finding. For the first four days following nerve section no fibrillation is observed in the denervated muscle. Its first appearance is in the form of scattered single and very small momentary indentations of the surface of the muscle. Each is accompanied by a single very small diphasic action current (fig. 2). The electrical change is from 1 to 3 micro-

[1] The operation and subsequent decerebration were performed by one of us (D.D-B.) in the department of the Research Unit, the National Hospital. We are grateful for the facilities allowed us by Dr. Carmichael for this purpose.

volts, but this value is purely relative with needle electrodes. Each twitch can be observed, both by the eye and in the electrical record, to recur at intervals of about two seconds. Fibrillation differs not at all in red and pale muscle fibre in the cat (fig. 3), as also was noted by Langley and Kato (1914-15). These colour differences, which have been found to be concerned with muscular functions other than the contractile process, (Denny-Brown, 1929*a*) are not affected by the atrophic process until its later stages. When the whole belly of a muscle such as soleus in the cat is observed each indentation is seen to be a momentary tightening in the whole length of a very small part of a muscle fasciculus. It would appear to be the repeated twitching of a single muscle fibre with accompanying very small action current at intervals of two to ten seconds (cf. fig. 2). Fascicular twitching does not occur.

On the fifth and sixth days few fibres are twitching in this way, and the twitching appears to be confined to those few, the remainder being inactive. Thus only one fibre in a fasciculus may be concerned. On the seventh and later days all fibres are found to have entered upon this phase of recurrent isolated twitchings, and continue to twitch until the muscle is in an advanced state of wasting (fig. 3). We have not attempted to trace the termination of the process. Langley and Kato (1914-15) observed it up to seventy-one days from time of nerve section.

It is readily ascertained by direct visual observation of the surface of the muscle that the twitches in different fibres have no relationship to each other, the one fibre twitching at a particular rate quite independently of those near or far away. The twitching is inco-ordinate. The final state of confused agitation and the confused action currents of fully developed fibrillation are therefore the result of the combined effect of the irregular mechanical and electrical disturbance in thousands of individual muscle fibres (fig. 3). In this state it is occasionally possible to observe that one particular twitch or action current is being repeated at intervals of about two-fifths of a second (fig. 3*b*). Grouped twitching does not occur until drying or mechanical factors intervene. The electrical action currents become more feeble as the muscle becomes more atrophied.

The appearance of the phenomenon of fibrillation after denervation is associated with the development in degenerating mammalian striped muscle of a particular sensitivity to acetylcholine on the fifth day after denervation, as described by Frank, Nothmann and Hirsch-Kauffmann (1922). The muscle may then enter a spasm of contraction on exposure to an extreme dilution of acetylcholine. Afferent nerve fibres, identical with antidromic vasodilators, distributed in muscle (Hinsey and Gasser,

1930) can by antidromic action liberate a contracting substance, probably acetylcholine, although it is not inhibited by atropine (Frank, Nothmann and Hirsch-Kauffmann, 1922, and Dale and Gaddum, 1930), but fibrillation and atrophy continue in the absence of any sensory or sympathetic innervation. On the other hand, the presence of remaining sensory and sympathetic innervation does not materially alter the process of atrophy in animal experiment (Sherrington, 1894) or in the process of disease in man (poliomyelitis).

It was at first thought that the contracture produced by acetylcholine was not accompanied by action currents (Riesser and Steinhausen, 1923). Schäffer and Licht (1926) and Brown (1937) have found that the contracture is accompanied by fine action currents and have noted that the drug enhances fibrillary contractions. Brown has shown that these small action currents appear with smaller doses, and with a large dose the contracture lasting five to ten seconds occurs, and that this phenomenon is free from action currents. It therefore appeared possible that natural fibrillation may be due to natural acetylcholine.

We observed that a drop of saline containing acetylcholine, diluted 1 : 500,000, allowed to fall on the surface of a muscle just commencing to fibrillate on the seventh day after nerve section, brought about an immediate local contraction lasting some twelve to twenty seconds (fig. 4*b*). As the contraction subsided all the muscle fibres in this area remained fibrillating for many minutes, and gradually the disturbance passed *by imperceptible transition* of moderate fibrillation into the original state of a few isolated fibres fibrillating (fig. 4*c*). Acetylcholine contracture appears therefore to be an intense contraction process of the same essential nature as the phenomenon of fibrillation. It therefore appears likely that true fibrillation is due to the sensitization of the denervated muscle fibre to the small amounts of acetylcholine in the circulating blood. In this connection it is of interest that Langley and Kato (1914-15) noted that physostigmine (eserine) markedly enhances fibrillation in denervated muscle, but was without effect before the fifth day. In view of the effect of eserine in inhibiting the natural destruction of acetylcholine in the tissues this observation strongly supports our contention that the fibrillation from acetylcholine is not only indistinguishable from spontaneous fibrillation but is identical with it.

Langley and Kato (1914-15) further observed that a different, coarser, twitching is caused by eserine in the *normal* mammalian nerve-muscle preparation. This, they maintained, is really fascicular, each a twitch in many muscle fibres co-ordinated by a nerve fibre, for this type disappears

twenty-nine hours after nerve section, at the time that excitation of the divided nerve first fails to reach the muscle (Langley and Kato, 1914-15, Titeca, 1935). Curare abolishes this effect of eserine. Titeca (1935) has shown that the excitability and conductivity of the nerve begins to wane only on the third day following section, and he places the first point of failure of transmission at the end plate where signs of degeneration begin to appear at the end of twenty-four hours (Huber, 1900, Boeke, 1911, 1921). Therefore it appears necessarily to follow that in the normal nerve-muscle preparation eserine acts on the nerve fibre or nerve fibre termination, but not on the receptive substance or muscle fibre. Acetylcholine also produces similar twitchings in normal muscles (Bender, 1938) with previous injection of a small dose of eserine. The gap of four days in which acetylcholine and eserine fail to stimulate muscle after nerve section would appear to us to be strong argument against the former being the normal transmitter between nerve and muscle.

Langley (1915-16*b*) considered this eserine fasciculation to be an enhancement of a similar phenomenon observable in normal muscle at a certain stage of fatigue, a phenomenon in the light of recent knowledge also possibly attributable to accumulation of acetylcholine near the nerve fibres, but he did not take steps to exclude polarization of electrodes. Until the latter can be excluded it is not possible to decide this point.

Bender (1938) has observed transient contracture of the denervated facial and ocular muscles in monkeys, induced by fright, and the enhancement of this reaction by eserine. This indicates that free acetylcholine can be present in the general circulation, for adrenalin and other substances do not produce the effect. The animals were observed intact, so that true fibrillation could not be seen. The gradual indistinguishable transition we have described from acetylcholine contracture to fibrillation indicates, in our view, that the latter is only a very mild degree of the former, and that smaller amounts of the substance must be present in the normal circulation.

We would conclude, therefore, that the fibrillation of muscle undergoing atrophy as a result of denervation is due to periodic rhythmical twitch excitation of each muscle fibre sensitized by neural atrophy. The source of the excitation would appear to be the small amounts of acetylcholine in the normal circulation. We would refer to this phenomenon as "true fibrillation," to distinguish it from other more coarse varieties of muscle twitching to be mentioned below. Such true fibrillation occurs in all voluntary muscles deprived of motor nerve supply. From observations on wasting muscles resulting from diseases affecting motor neurones

it would appear that intact sensory nerves to muscle do not influence the phenomenon. In most patients with wasted limb muscles from neuritis or poliomyelitis this fibrillation cannot be observed by clinical examination. When, however, the subcutaneous tissue is unusually thin these muscles can be seen to present the fine characteristic fibrillary tremor. In electromyographic observations (with Dr. S. Nevin) of the wasting muscles of patients suffering from muscular dystrophies including dystrophia myotonica, we have not observed true fibrillation.

(4) The Fasciculation of Muscle in Motor Neurone Disease.

Involuntary twitching of muscles has long been recognized as a feature of the course of amyotrophic lateral sclerosis, and its subvarieties, bulbar palsy and progressive muscular atrophy.

"The muscles whose nutrition is threatened, or actually damaged, are often jerked by little fibrillary or partial contractions. When this takes place the skin is seen to be raised and depressed as if by the tightening and loosening of delicate cords acting in the direction of the muscles. These contractions are of short duration, but they succeed each other with tolerable rapidity (at intervals of from one to four seconds) and occur in many points of the surface of the muscle. At other times the muscles are agitated with little worm-like movements. In some patients these contractions are almost continuous and occupy a whole limb or a great part of the surface of the body, while in others great attention is necessary to prove their existence, owing to their rarity and weakness, and often they need to be provoked by voluntary or electric stimulation, or by compressing or pinching the muscles. After such stimulation the reflex fibrillary contractions are stronger and more numerous. Partial or fascicular spasmodic contractions sometimes cause little movements of the limbs, especially of the fingers or thumb. Like the foregoing they are short and intermittent, but more rare." (From Duchenne, "L'Electrisation Localisée," third edition, p. 486, from Selections from the Works of Duchenne, Poore, 1883, London.)

In the brief periods of arrest characteristic of the disease, such twitching may disappear for weeks or months at a time. Where it occurs in flat muscles such as pectoralis major it can be readily seen that each twitch involves a bundle of muscle fibre 1 to 3 mm. or more wide, and is a sharp single contraction of that bundle, producing a momentary tightening of its whole length. When the twitching is not too intense it can also be observed that a particular bundle twitches steadily at a particular rate, which varies from one to another with long intervals of

five seconds to two minutes. Where the twiching is intense the whole muscle is in continual coarse agitation and the twitching of it in any one place may appear to affect a large muscular bundle in different ways. Each particular shape of twitch is, however, repeated in exact manner after an interval.

In muscles which are extremely wasted, and covered only by a very thin layer of skin and subcutaneous tissue, such as the tongue or the first dorsal interoseus muscle of the hand, this coarse twitching may be seen to be combined with and later replaced by a fine " true " fibrillation such as has been described above for denervated muscle.

Electromyographic records of muscle in this state of coarse twitching (figs. 5 and 6) show that each fascicular twitch is accompanied by a single large action current. In a long strip of record it can be seen that both the mechanical deformation of the muscle surface, and the accompanying shape of the action current, are individual for each twitch and that each particular combination is repeated again and again at long intervals, such as 4·9 and 6·8 seconds for that shown in figs. 5 and 6. Where the twitching is too complex to identify individual twitches by the naked eye, the electromyographic and mechanical records still show that any one shape of twitch is repeated at relatively long intervals (figs. 7 and 10).

The regularity in position, size and shape of action current of each involuntary twitch of the " fasciculation " of this disease points to its being a *single impulse contraction in a fixed group of muscle fibres.* The group is smaller than a muscular fasciculus, but much larger than one single muscle fibre. The only functional group of this nature in muscle is the motor unit. If this twitching were the result of the reception of a nerve impulse by the whole group of muscle fibres supplied by a motor nerve fibre, it would follow that the origin of the impulse must be related either to a pathological process in the nerve fibre itself, or in the parent anterior horn cell. From the pathology of this disease we can suspect the latter.

This phenomenon, commonly called " fibrillation," but more properly called *" fasciculation,"* may therefore represent the intermittent involuntary discharge of single nerve impulses by an abnormal motor neurone. These abnormal action currents are in fact comparable in size and shape to the individual discharge of single moderate sized motor units. By instructing the patient to contract the muscle slightly by involuntary effort, the characteristic rhythmical discharge of normal motor units can be made to appear in the electrogram, accompanying the contraction. A strong or moderately strong willed contraction is accompanied by a con-

fusion of action currents, but by arranging that a very weak contraction is produced, a few simple action current rhythms can be obtained (fig. 11). Discharge provoked in this way is a rhythmical series of nerve impulses at a rate of five to twenty-five a second. The resulting muscular contraction is a partly fused series of twitches, but the action currents, being much more brief, appear as a regular series of identical shape.

It was of interest to observe if a motor unit which showed "fasciculation" could be excited to normal willed discharge. Normally the *same* motor units always begin the discharge in a very slight muscular contraction—apparently particular units are always the first to contract in the beginning of that particular willed movement. We searched for "fibrillating" units which could thus be possibly called into activity early in slight voluntary movement, and in due course found several examples (fig. 8). Here there was no doubt that the disordered motor neurone could also discharge a normal series of identical nerve impulses in response to willed effort. It is presumed that the other fasciculating units also did so but came so late into contraction that their discharge was swamped in the resulting intensity of electrical fluctuation. The units observed in this way were fasciculating at moderately long intervals of five to thirty seconds. Voluntary discharge of this type enhances the "fibrillation" so that in the few seconds following the movement fasciculation is more rapid in that particular unit. This appears to substantiate our conclusion that the site of the abnormality leading to the involuntary twitching is closely related to the excitable portion of the neurone, the cell membrane or the synapse. The disorder is not *directly* related to the process of excitation, for these units are neither more nor less readily excited by voluntary effort than is any random unit sampled by the electromyogram. Their discharge was regular and not subject to abnormal lapses or ease of fatigue. We also observed that percussion and cooling enhanced fasciculation, apparently by also inducing a light voluntary discharge. On account of the naked-eye resemblance of early shivering to this twitching, we do not recommend these procedures for facilitating the observation of the disorder in the clinic, though the electromyographic record is distinctive in shivering (Denny-Brown, Gaylor and Uprus, 1935), being a grouped tetanic discharge.

In the course of a willed movement of moderate degree of any one muscle group at a joint, there occurs complete cessation of tonic and other action currents in the directly antagonistic muscle group. This is not necessarily true for contraction of synergists, but the discharge of the motor neurones is inhibited in the course of direct reciprocal innervation.

We have observed that the motor unit discharge of amyotrophic lateral sclerosis cannot be inhibited in this way by willed contraction of a direct antagonist as prime mover (fig. 9). We have therefore demonstrated that "central excitatory state" (Sherrington, 1929) can be set up, and the neurone thus caused to discharge naturally, and "central inhibitory state" is unaffected and does not interfere with fasciculation. These processes are related to the synapse. It is to be concluded that the disorder underlying fasciculation is situated in the cell body or its dendrites and not at or outside its surface, and is a precursor of atrophy of the neurone.

In wasting muscles the coarse fasciculation and fine fibrillation are concomitant, which is to be expected from the known true degeneration of the motor neurone which eventually occurs. Here the contrast between the size of the action currents of fibrillation and fasciculation can be seen in the same record (fig. 10). With needle electrodes only a small electrical field is sampled and the difference in size between muscle fibre action current and motor unit action current is therefore relative and not absolute.

(5) Fascicular Tremor Appearing with Contraction ("Contraction Fasciculation").

Coarse tremors of fasciculi in limb muscles are often observable in subjects of wasting diseases. Such tremor is liable to confusion with the spasmodic fasciculation of amyotrophic lateral sclerosis described above, especially since it may occur in combination with it in that disease, or alone in other affections, or with true fibrillation following poliomyelitis or polyneuritis. It is quite independent of either "true fasciculation" or "true fibrillation" in that it disappears completely with complete relaxation of the muscle.

In characteristic form it is seen as a coarse rhythmical tremor of a fasciculus at a rate of from 5 to 20 a second. The contraction is strong enough sometimes to cause wavering of an extended finger. With stronger contraction other fasciculi show similar tremors, but with moderate to maximal contraction the twitching grows more rapid and may be swamped by the contraction of other fibres in the muscle. In muscles such as pectoralis it can be observed that the contraction involves only part of a fasciculus.

In myographic records the twitching is a regular discharge exactly comparable to that of a motor neurone, though the resulting twitches of the muscle are poorly fused even at higher rates of discharge (figs. 12*b*, 12*c*). The individual mechanical twitches are much larger than those of

the usual motor units to come early into action in a willed movement, and their discharge is not so rapid. The onset is always at a certain stage in a particular movement in the muscle concerned, sometimes with only slight postural contraction (fig. 12*a*). The phenomenon is encountered in our experience only where the muscle is notably wasted, but would appear to be the normal discharge of a very large motor unit.

The tremulous motor unit is not necessarily the first to discharge in contraction and when different muscles are observed the tremor is seen to enter the contraction at different stages. As has been stated above, a particular voluntary movement appears to begin always with discharge of the same motor unit. More intense contraction is secured by the addition of more and more units added in a particular sequence (fig. 11). This "recruitment" of motor units into willed contraction is identical with that occurring in certain reflexes (Liddell and Sherrington, 1923, Sherrington, 1929). The early motor units in normal gradual voluntary contraction are always in our experience small ones (fig. 11). The larger and more powerful motor units, each controlling many more muscle fibres, enter contraction late. In a muscle wasted by loss of many motor neurones graduation of contraction becomes uneven because large motor units become active without sufficient previous recruitment of small units to smooth their contraction. That they are contracting in the same manner with the rest of the muscle in a normal individual is indicated by the size of the action currents in intense contraction. Their frequency corresponds with that of the muscle sound (15 to 35 a second (Wollaston, 1810)) and appears to us its probable explanation.

We believe that the isolation of large motor units by relatively preponderating atrophy of small ones is an explanation which best serves the facts of "contraction fasciculation."

(6) Coarse Local Tetanic Fasciculation ("False Fibrillation").

Clinicians recognize types of benign "fasciculation" or "fibrillation," which occur in muscles not subject to a wasting disease. Of these a twitching of the orbicularis oculi of the lower lid with fatigue or debility is one type within general experience. Occasional very localized twitching in a calf muscle is also common, and a more generalized form affecting the calf muscles and the small muscles of the feet and hands is described as "myokymia" after Schultze (1895) and Kny (1888). In the latter condition irregular contractions of fasciculi of muscles gives a slow undulation of the surface.

This type of contraction has a longer duration than that of the forms

of fibrillation described above. For some one to three seconds the contraction pursues either rapidly interrupted course as is common in orbicularis oculi, or a deliberate sustained spasm. The contraction appears in the same place at irregular intervals, and is often large enough to make the subject conscious of its occurrence, and he cannot suppress it. It is not related to willed movement.

The *sensation* of twitching appears to result from the size of the structure involved, for other fibrillation is sensible according to its size, and in the type with which we are concerned here the structure involved is of the size of a whole fasciculus.

Records of such twitching confirm the impressions gained from visual observation. Both in the calf (fig. 13) and in orbicularis oculi (fig. 15) the twitch is in fact a partly fused muscular tetanus with repetitive nervous discharge which is irregular in time interval, and often in shape as well. The irregularity in shape of successive action currents points to a focus of irritation which is not nervous, but affects unevenly a bundle of nerve fibres to the fasciculus.

In a patient suffering from generalized myokymia, associated with cramps of the legs ("paramyotonia") we obtained records of both phenomena (fig. 14). In myokymia a fasciculus is suddenly involved in intense high frequency discharge lasting one-twentieth to one-tenth of a second (fig. 14*a*). The resulting contraction is a slow wave. This type of contraction occurs in different fasciculi independently and intermittently. A cramp takes the form of rhythmical high frequency discharge of this kind (fig. 14*b*). We observed the transition of the action currents of willed movement into periodic intense cramp action currents (fig. 14*c*). Occasionally the intense discharge will last a second or more without intermission, and then cease suddenly (fig. 14*d*) or become transformed into the intermittent type. The contraction is fascicular, and in our view is but an intense form of the fasciculation of fatigue (fig. 13).

While further examination of the focus is beyond the means at our disposal, we regard this phenomenon of "false fibrillation" and "myokymia" as one probably related to vascular cramp, or other change in the vessels which supply the fasciculus. Cramps in the same muscles commonly affect the subjects of myokymia. It has not in our experience been relieved by calcium, though improvement in the general health of the subject usually leads to its disappearance.

It is noteworthy in this connection that on the one hand Langley (1915-16*b*) noted that fascicular contraction occurred in frog muscle at a moderate stage of fatigue, and that on the other Kny and Schultze both

noted in generalized myokymia that their patients suffered from greatly enhanced sweating. Excessive perspiration was also a disorder obvious in the two patients suffering from generalized myokymia observed by us. These observations indicate that fatigue may derange the excitability of the motor nerve in or near the muscle, and that disturbance of sodium chloride balance may in particular cause such derangement, in other forms than cramp. It may be stressed therefore that the incomplete relief of the condition by exhibition of sodium chloride indicates that the neurosis or exhaustion state underlying fatigue or hyperidrosis requires also to be treated in patients subject to this disorder.

(7) Involuntary Multifascicular Contraction in Affections of 7th Nerve.

The muscles supplied by the 7th cranial nerve are peculiar in that in stages of partial *regeneration* of the nerve a curious type of involuntary contraction and spasm appears (" post-paralytic contracture "). This is not " true fibrillation " for intermittent very small action currents in the electromyogram of the *completely* paralysed muscle indicate that " true fibrillation " is present, though not observable by inspection of the face by the clinician. Post-paralytic contracture is commonly observed following Bell's palsy and was described by Duchenne (1883). Babinski (1905) and Lamy (1905) observed the association of the spasm with inco-ordinate movements of the face, such as contraction of the frontalis when attempting to close the eye, and considered it to result from regeneration of the nerve fibres into abnormal channels. The exact manner of production of the spasm remains unexplained. It can be observed as intermittent flickering contractions, one contraction often affecting wide areas of the facial muscle, and each contraction varying from some half to five seconds in duration. By the overlapping of successive contractions moderately steady " contracture " is set up. When the phenomenon is slight in degree it may be seen only as momentary dimpling of the chin. It is not infrequently observed as a sign of affection of the 7th nerve by tumours in the lateral recess, and we have seen it occur as the first sign of a pontine attack of disseminated sclerosis, as is also described by Oppenheim (1911) and others. " Post-paralytic contracture " is quite distinct from psychogenic facial spasm, which is a stereotyped movement related to the tics.

Electromyographic records of " post-paralytic facial contracture " reveal successions of very rapid action currents of uniform size and shape (fig. 16). The size and regularity of each outburst is exactly comparable with motor neurone discharge, though the rate of discharge is greater than that of

motor neurones in limb muscle. The outbursts occur at irregular intervals of one to thirty seconds or more. They are of increased frequency following any voluntary contraction of the muscle, and appear to affect the same nerve fibres as are innervated voluntarily, for an attempted movement causes these units to discharge also. These bouts of rapid discharge are periodic, as if a focus in the nerve fibre, or the motor neurone in the facial nucleus were intensely excited at intervals. We have not found any criterion to give a clue to the site of origin of the discharge. The electromyogram of this post-paralytic contracture closely resembles that of stretch responses in sodium contracture in muscle (Adrian and Gelfan, 1933) though in the face the discharge is nervous. Possibly the facial muscle is particularly sensitive to stretch in this way at a particular stage in regeneration. The electromyogram nevertheless indicates its fundamental difference from true fibrillation and true fasciculation, and the other forms described above. The electromyogram of tic-like facial spasm on the other hand is that if any voluntary movement in the face.

Bender (1938) in an interesting paper shows that the paralysed denervated facial muscles of the monkey enter a spasm when the animal is frightened. It is concluded that the phenomenon is acetylcholine contracture due to release of that substance into circulation by fright. Such contracture affects all the facial muscles at once, and disappears when regeneration occurs. In this manner it differs entirely from "post-paralytic contracture," which appears only with regeneration and affects isolated fasciculi. We have not observed this fright phenomenon in man.

(8) On Some Abnormal Contractions Elicited by Mechanical Stimulation of Voluntary Muscle, and their Relation to Fibrillation.

Schiff (1858) described the contraction elicited in striped muscle by direct percussion ("idiomuscular contraction") and the persistence of the phenomenon in the animal recently dead. A localized knot of contraction immediately forms at the site of percussion, and series of small waves of contraction leave the knot on either side and travel to the ends of the muscle fibres, sometimes being reflected back again. Schiff and others have argued that these localized and slowly transmitted forms of contraction were related to the sarcoplasm and not to the sarcostyles (Joteyko, 1909). Langley and Hashimoto (1918-19) observed slow waves passing in both directions from a focus in a degenerating muscle fibre, but the phenomenon is rare as a spontaneous event in atrophic muscle. Its appearance immediately after death appears to be related to deficient oxygeneration

for it can be produced readily by sodium sulphocyanide (Langley, 1915-16c) though other sodium salts delay its appearance in excised muscle (Milrad, 1885-86). Curschmann (1905), Klippel (1903) and others have noted the phenomenon of idiomuscular contraction in man and its intensification, with the appearance of the slowly transmitted waves, in patients suffering from various debilitating diseases such as phthisis, alcoholism, acute rheumatism. In these it can be observed especially well on percussion of the pectoral muscles, and was at one time considered of importance in the diagnosis of phthisis, though direct relationship was later disproved (Klippel, 1903). The localized contraction was called by clinicians "myœdema" (myoïdème). Curschmann (1905) concludes that its occurrence is but one aspect of a generally raised muscular excitability which may occasionally affect the nerves also.

We have observed the fully developed phenomenon in two patients with wasting of the muscles of the shoulders as part of a general cachexia from neoplasm, but with no other sign of nervous disease. We submitted one to electromyographic examination of the anomaly for comparison with true fibrillation and fasciculation.

In the normal person percussion of muscle induces a small local knot of contraction with tightening of the remainder of the fasciculus, and both subside in from one to five seconds according to the intensity of the stimulus. A sudden plucking pinch, sufficiently strong to be painful, of the belly of biceps brachii elicits it well. The electromyogram shows a large number of irregular fine action currents, indicating that local diffuse excitation has occurred, varying in degree according to the local mechanical damage.

When the "idiomuscular contraction" is present the local contraction appears as above, but the local contraction ("myœdema") subsides completely only after some ten seconds or more. It is accompanied by a few usual rapid action currents (fig. 17*a*, at *x*), and with brief general tightening of the fasciculus. The small transmitted wave leaves the knot of local contraction immediately, and we have recorded it as it passes a distant point on the same fasciculus, all of which it appears to involve. It travels at a rate calculated to be 2·08 cm. a second and last 0·7 sec. at one point. It has no action current (fig. 17*a*), though there is possibly a small negative variation. If action currents of willed contraction are present they are not abolished by the slow wave (fig. 17*b*).

Gelfan and Bishop (1932, 1933) and Gelfan (1933-34) have shown conclusively that it is possible to excite slowly propagated waves in striped muscle of the frog by stimulating the *contents* of the muscle fibre, either

at its cut end, or by a localized mechanical stimulus. Such a slowly propagated contractile process was found not to be accompanied by an action current. These authors have proposed the reasonable hypothesis that the contents of the muscle fibre (sarcoplasm and sarcostyles inclusive) possess a separate irritability and rate of conduction. On this hypothesis the normal mechanism of conduction of the excitatory process very rapidly over the whole muscle fibre and rapidly stimulating the whole of it, is the "action potential mechanism." This appears to be a wave of depolarization passing over the sarcolemma, or outer muscle membrane, accompanied by an action potential. Thus normal contraction of a single fibre is rapid and possesses initial electrical variation.

On this view, which appears well founded, the phenomenon of idiomuscular contraction becomes the response of the whole muscle fibre to intense mechanical stimulation, and is made up of a momentary stimulation of normal twitch contraction, plus an intense and more lasting stimulation of the muscle fibre contents at the point of injury. This latter focus is the starting point of slow waves of contraction in the contents of the fibre. Under certain circumstances, among which the prominence of acute infections, gastric carcinoma, gastritis, and tuberculosis strongly suggest a factor of disturbed potassium : sodium ratio, the excitability of both sarcolemma and muscle fibre contents appear to be raised. We might therefore recognize in the phenomenon of idiomuscular contraction a disturbance of the excitability of the muscle fibre, predominantly of its contractile contents. In contradistinction, true fibrillation is a greater sensitization of the "action potential mechanism" (? sarcolemma).

Bremer (1932) has shown that the various varieties of physiological and pharmacological contracture in muscle can be related to two types of excitability normally present in muscle and our view of the phenomena of fibrillation and idiomuscular contraction would fall into line with this point of view, though we have not attempted to determine the excitabilities concerned.

In the earlier sections of this paper we have indicated that the clinical observation of fascicular twitching on the one hand and true fibrillary twitching on the other may be interpreted as due to enhanced irritability of the motor neurone, or the muscle fibre respectively. The occasional occurrence of fasciculation in the course of an acute toxic infection such as the onset of pneumonia, in association with enhanced idiomuscular contraction, would indicate that in such states the irritability of all the various parts of the motor unit may be disturbed. Such is also more commonly and consistently observed in the course of tetany, where fascicu-

lation may be observed to lead up to enhanced reflex excitability of the motor neurone (West, 1935), and where enhanced idiomuscular contraction has been described (Curschmann, 1905).

Conclusions.

(1) Close inspection of spontaneous twitching of muscle fibres reveals characteristics which enable the situation of the disturbance of excitability to be deduced. The single discharges of disordered anterior horn cells are thus distinguishable from the more coarse and longer twitches arising from affections of the intramuscular nerves, and both are distinct from the fine fibrillation of denervated muscle. Combinations of the various types may occur.

(2) Hyperexcitability of motoneurones in diseases such as progressive muscular atrophy or amyotrophic lateral sclerosis results in regularly periodic discharges of single impulses by the motor neurone. The focus of irritation is not at the synapse, but within the neurone. The resulting fasciculation at rest should be distinguished from rapid fasciculation during contraction ("contraction fasciculation").

(3) Denervated muscle fibres contract periodically, and the confused medley of small twitches constitutes true fibrillation. The movement is so slight that it can seldom be seen in the clinic. The twitching appears to be due to heightened excitability of the sarcolemma, or rapidly conducting portion of the muscle fibre, to traces of free acetylcholine in the tissues.

(4) Re-innervated muscle is free from such involuntary excitation, except for the curious "contracture" of facial muscle, which consists of periodic intense repetitive discharge which suggests a central mechanism.

(5) In circumstances of fatigue or excessive loss of sodium chloride involuntary muscular contractions appear. Those due to fatigue are small bursts of contraction in a fasciculus, and are of a type such as would be caused by irregular discharge spreading to and through all the nerve bundles in the fasciculus. Those of myokymia, associated with hyperidrosis are of similar nature but of more widespread distribution, and more intense discharge. Both are clearly related to muscular cramp. The prolonged discharge, compared with the single twitch of fibrillation and the fasciculation of neurone discharge, gives the resulting fascicular movement a slower, undulating appearance.

(6) The excitability of the cytoplasm of muscle fibres may be disproportionately raised in association with cachectic states. Abnormalities of

the mechanical excitability of the muscle fibre then appear. Investigation of the sodium : potassium ratio in this connection would appear desirable.

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PLATE XVI.

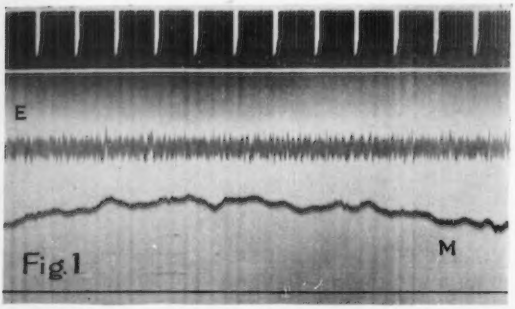


Fig. 1

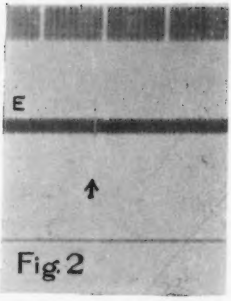


Fig. 2

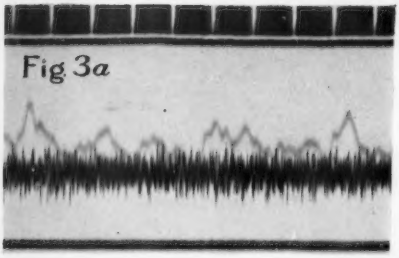


Fig. 3a

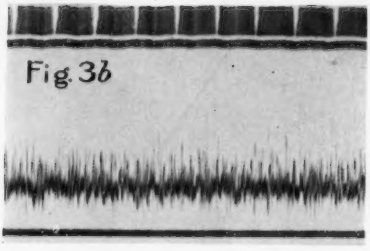


Fig. 3b

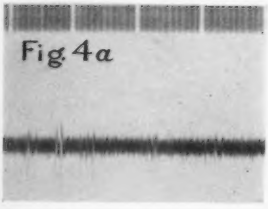


Fig. 4a

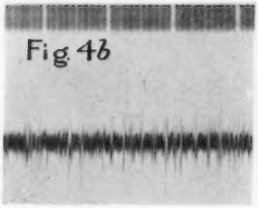


Fig. 4b

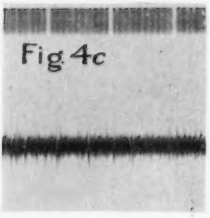


Fig. 4c

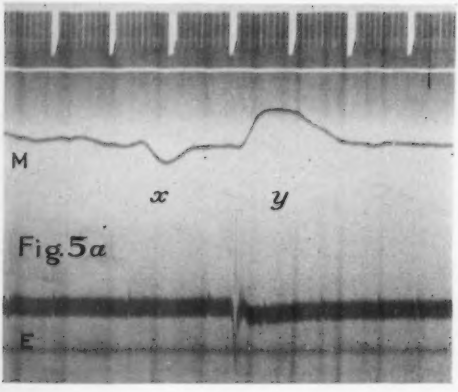


Fig. 5a

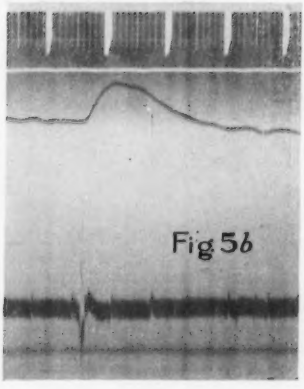


Fig. 5b

To illustrate article by D. Denny-Brown and J. B. Pennybacker.

PLATE XVII.

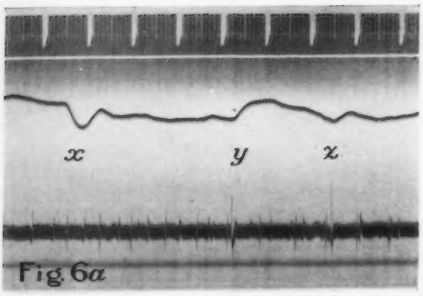


Fig. 6a

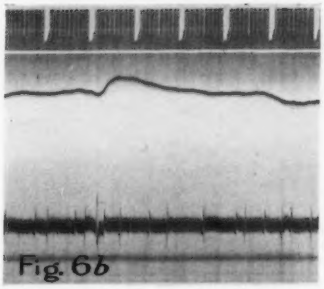


Fig. 6b

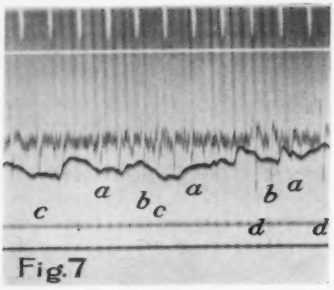
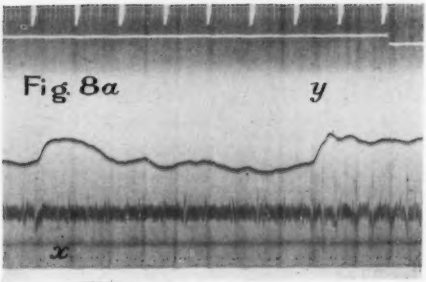


Fig. 7



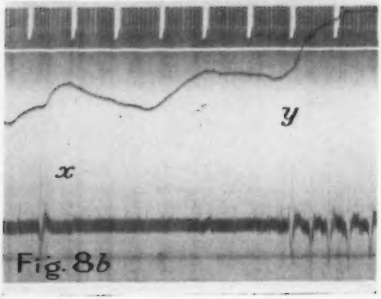


Fig. 8b

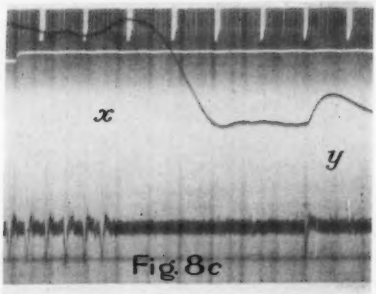


Fig. 8c

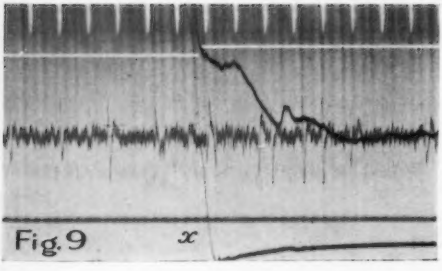
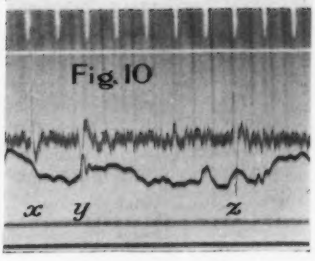
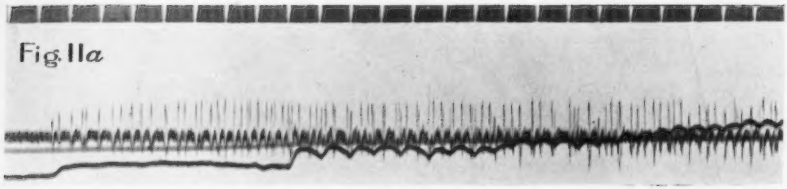
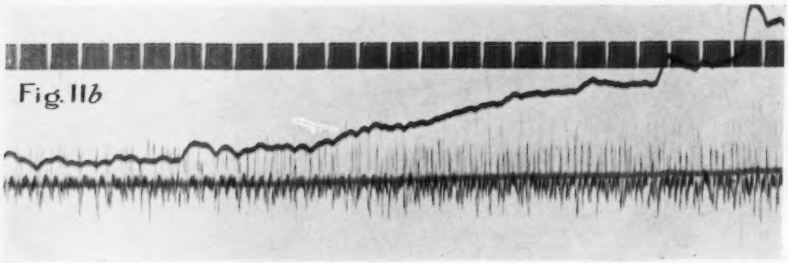


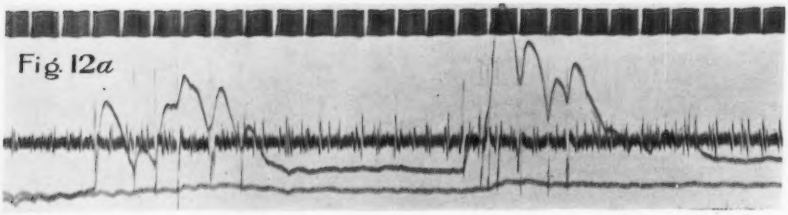
Fig. 9

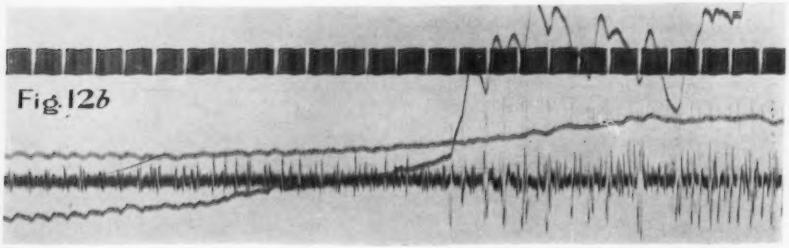


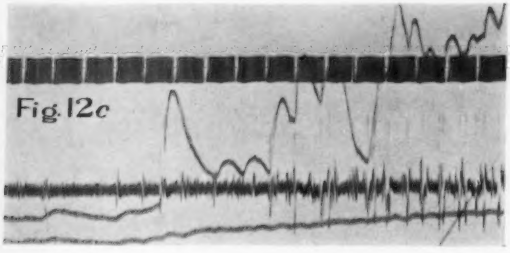
To illustrate article by D. Denny-Brown and J. B. Pennybacker.

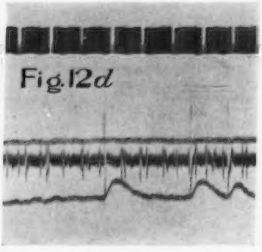




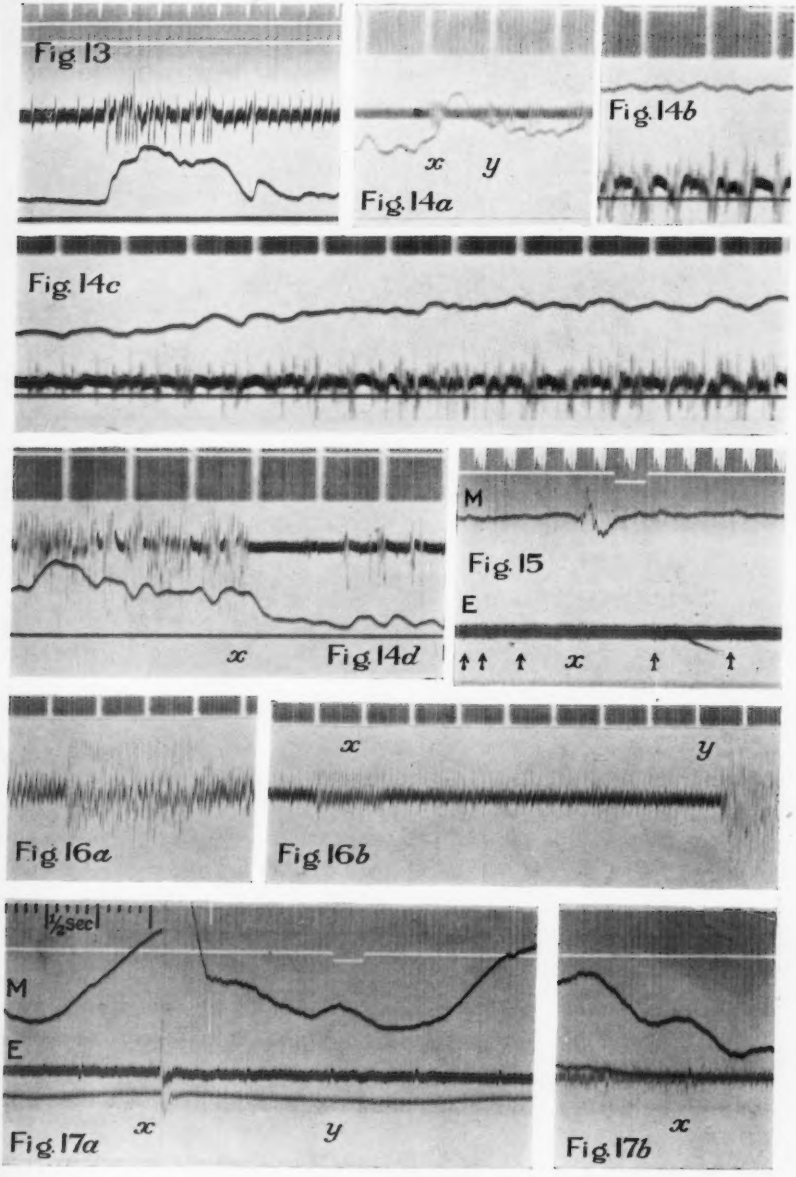








To illustrate article by D. Denny-Brown and J. B. Pennybacker.



To illustrate article by D. Denny-Brown and J. B. Pennybacker.

DESCRIPTION OF PLATES.

All tracings read from left to right. Time marked by vertical lines at top of each record at 1/5 sec. intervals (except fig. 17).

PLATE XVI.

FIG. 1.—Mechanical (M) and electrical (E) tracing from the mylo-hyoid muscle of a patient suffering from wasting of the muscles of the tongue due to syringomyelia. The fibrillation was visible just under the mandible, where the muscle lies just under the skin. The vertical white strokes at the top of the record indicate intervals of 1/5 sec.

FIG. 2.—Electrical record from M. soleus, six days after section of sciatic nerve. Cat. Action current of fibrillation at arrow. This action current was repeated at intervals of 5·6 sec.

FIG. 3*a*.—Mechanical and electrical record of fibrillation in M. soleus, cat, nine days after section of sciatic nerve.

FIG. 3*b*.—Electrical record of intense fibrillation in M. gastrocnemius nine days after section of sciatic nerve.

FIG. 4.—In 4a is shown the action currents of soleus seven days after nerve section. Some four seconds later about 0·1 c.c. of 1 : 500,000 acetylcholine in saline is injected into the muscle at its origin. The reaction after about a second is shown in fig. 4*b*. Thirty seconds later the electromyogram is that shown as Fig. 4*c*. Cat. Time 1/5 sec. intervals.

FIG 5*a*.—Left pectoral muscle of patient suffering from amyotrophic lateral sclerosis, with coarse fibrillation. Mechanical (M) and electrical record (E) of a fasciculus of the muscle. At *x* there occurs a twitch in the underlying intercostal muscle. At *y* a twitch occurs in the fasciculus with accompanying action current.

FIG. 5*b*.—As fig. 5*a*, showing an identical twitch and action current 4·9 sec. later. Time 1/5 sec. intervals between large white strokes.

PLATE XVII.

FIG. 6*a*.—Pectoralis muscle of patient suffering from amyotrophic lateral sclerosis. Slight postural contraction is present, with rhythmical discharge of three small motor units. At *x*, *y*, and *z*, there occur three fascicular twitches. That at *x* is in the underlying intercostal muscle and is without action current. Those at *y* and *z* occur in the fasciculus from which the record is taken, and are different in both the mechanical and electrical record.

FIG. 6*b*.—A continuation of the record of fig. 6*a* showing repetition of the twitch *y* of record 6*a* after an interval of 6·8 sec. Time intervals of 1/5 sec.

FIG. 7.—M. triceps of patient suffering from amyotrophic lateral sclerosis in advanced stage. Showing rapid coarse fasciculation and fine fibrillation. The muscle was very weak and atrophic. In the confused electromyogram various shapes of action current marked *a*, *b*, *c*, *d*, are being repeated at intervals varying from 0·5 sec. to 10·0 sec. and longer.

FIG. 8.—M. pectoralis major. Amyotrophic lateral sclerosis. In fig. 8*a* a spontaneous fascicular twitch occurs at *x*. At *y* the patient commences a slight willed movement, with resulting repetitive discharge and contraction of the same motor unit. In fig. 8*b* a similar twitching unit in another part of the muscle is seen at *x*, and its discharge in response to willed effort at *y*. The action currents are identical. In fig. 8*c* the same voluntary discharge as in fig. 8*b* is seen terminating 1·8 sec. later. Enhanced fibrillation begins at *y*, and for three irregular beats occurred at intervals of about 0·6 sec. on the continuation of the tracing after *y*.

FIG. 9.—M. triceps. Amyotrophic lateral sclerosis. Severe fasciculation. The patient was strongly innervating the flexors of the elbow before the record begins. He ceases at *x* and relaxes. Coarse fasciculation and fibrillation occur irregularly during the effort, which abolished all central discharge of other kind in the muscle. The fasciculation is a little more frequent in the first second following reciprocal inhibition and then settles down to the usual irregular rhythm.

FIG. 10.—M. triceps. As fig. 7. Showing various types of twitch of one large fasciculus in an advanced stage of the disease. That marked *x* had occurred 4·4 sec. earlier and was repeated 5·4 sec. later. That marked *y* had occurred 4·8 sec. earlier, and recurred 5·4 sec. later. That marked *z* had occurred 8·2 sec. earlier and recurred 2·3 sec. later.

PLATE XVIII.

FIG. 11.—A normal voluntary contraction of M. biceps brachii. In the electromyogram the rhythmical discharge of motor units is seen to become more intense by the addition of further separate rhythms, each in a slightly larger size of action current. After a lapse of 2·2 sec. the record of fig. 11*a* is continued as fig. 11*b*, showing further increase of the movement by accrescence of further and larger electrical and mechanical units. Time 1/5 sec.

FIG. 12.—M. biceps. From a patient with progressive muscular atrophy, showing at this time only fasciculation during muscular contraction. The muscles were wasted. Fig. 12*a* shows occasional periodic twitching during a slight posture. Fig. 12*b* shows the twitching in another unit coming late into a willed movement. Fig. 12*c* shows the twitching occurring early in another willed movement. Fig. 12d shows occasional isolated twitches with slight movement such as holding the limb forward.

PLATE XIX.

FIG. 13.—M. biceps brachii. Patient with general asthenia. A coarse fascicular wave of contraction lasting a second is recorded on a background of slight postural discharge (one unit recording). Time 1/5 sec.

FIG. 14.—M. gastrocnemius. Patient with myokymia and cramps in both lower limbs. In fig. 14*a* a wave of myokymia occurs at *x*, accompanied by very rapid discharge in the electromyogram lasting 0·4 sec. Some slight normal discharge occurs at *y*. In fig. 14*b* is shown the electromyogram of an intense cramp, with periodic high frequency discharge. The patient was endeavouring to relax the muscle without success. In fig. 14*c* a voluntary movement develops into a cramp, with change of a normal action current rhythm into high frequency discharge. In fig. 14*d* a cramp is seen to end suddenly at *x*.

FIG. 15.—From a patient suffering from debility, with involuntary twitching of the lower eyelid. A small series of jerks in the mechanical record (M) is accompanied by a small repetitive action current, one to three diphasic waves in very rapid succession. Each group is indicated by an arrow. At *x* the patient blinked.

FIG. 16.—Facial palsy with partial recovery. Fig. 16*a* shows one of the frequent action current discharges which accompanies the spasm. The muscle is also fibrillating. Fig. 16*b* shows a motor unit discharging in slight voluntary expression involved in a bout of spasm at *x*, and entering intense discharge with other units at *y* in response to the command, "show your teeth."

FIG. 17.—Patient with cachexia from carcinoma. M. pectoralis major. Myogram from strenal end of a fasciculus, and electrical leads from this point also. A slow regular fluctuation in the myogram (M) is due to respiration. At *x* at the height of an inspiration the fasciculus is percussed heavily at a point 3·75 cm. away from the point recorded. The whole faciculus immediately tightens for 0·4 sec. after one large action current. 1·8 sec. later a wave, which had been observed to leave the point percussed, reached the electrode, an observer depressed a signal key to show he had seen it arrive. The hump in the myogram at *y* records its passing. There are no fresh action currents at this time. The electrocardiogram appears faintly in the record. The time marker lines are faint, and a period of 1·5 sec. has been stressed in tenths at the beginning of the tracing. In fig. 17*b* a similar wave is recorded during slight voluntary contraction. The action currents of voluntary contraction are unaltered by the wave.

Notices of Recent Publications.

The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects. By W. E. Le Gros Clark, J. Beattie, G. Riddoch and N. M. Dott. Edinburgh: Oliver and Boyd. 1938. Pp. 211, figs. 104. Price 12s. 6d.

The hypothalamus has for the time captured the interest that in recent years was enjoyed by the corpus striatum, the peripheral autonomic system and—still more ephemerally—by the so-called "premotor cortex." The present symposium of lectures delivered under the auspices of the Ramsay Henderson Trust by the authors named above will provide a useful summary of modern knowledge and current views. The anatomical section contains a clear, comprehensive and well-illustrated account of the comparative and human anatomy of the hypothalamus and hypophysis, while Professor Beattie contributes a précis of the experimental physiology of these structures. Dr. Riddoch summarizes the clinical manifestations of disease involving them, while Mr. Dott, with some unnecessary repetition of this matter, discusses the surgical treatment that may be possible. The last-named section will be of greatest interest to surgeons, and its superabundant illustrations will encourage them by that winning air of simplicity they impart to the necessary procedures.

The Brain and its Development. By J. Barcroft. Yale University Press, New Haven. 1938. Pp. 111. Price $2.

In these fascinating lectures Professor Barcroft traces the development of central nervous activity in the growing fœtus, relating this to the interaction between the internal and external media in which the fœtal brain finds itself. The chemical milieu that bathes the developing brain has a stability that reaches its highest refinement of regulation in man, a factor which the lecturer suggests as having in all probability played a part in the development of man's intellectual powers. The first indication of a disturbance of this stability is always an impairment of the highest qualities of the brain.

The ascending order in which the reflex mechanisms of the cord and the brain-stem are seen to take up their functions in the fœtus affords an interesting commentary on their activities in post-natal life, as these have been revealed by the experimental physiologist, while the successive disappearance of these functions from above downwards on successive descending transections of the neuraxis completes that picture of evolution and dissolution of function of which Jackson wrote.

The Doctrine of Signatures. A Defence of Theory in Medicine. By Scott Buchanan, Professor of Philosophy in the University of Virginia. London: Kegan Paul. 1938. Pp. 205. Price 7s. 6d.

This philosophical essay will have for the medical reader a paradoxical air, since it urges a return to the principles of Aristotle and Galen, the men who loomed so authoritatively, and as many think deadeningly, over mediæval medicine and science. But it is the ancient distinction between form and matter, and the rational and

teleological aspects of Galen's thought that are here put forward as the proper basis for speculative advance in medicine. Since psychiatry is the branch of medicine in which philosophical, and even metaphysical, issues are nearest the surface, there is much to confirm Professor Buchanan's sorrow that the popular philosophies which are so widely espoused by psychiatrists are not better understood as disguised and truncated Aristotelianisms: the sciences which grow precariously out of them, he says, fail at crucial points and frustrate their own rational developments. His brief references to homœostasis and "the pious talk about the unity and wholeness of the organism" are refreshing; confusion and loose generalization, while still widespread, are more easily spotted by such an outside observer, perhaps, than by doctors themselves. The author's plea for the revival of the liberal arts of the trivium and their application to medicine is lucidly and attractively expounded; it deserves the attention of those who are aware of the influence philosophical theories have had in the history of medicine and who are not blind to the crudities and culs-de-sac in some of the medical sciences to-day.

Les Arachnöidites Opto-chiasmatiques. Par J. Bollack, M. David and P. Pleech. Paris: Masson et Cie. 1937. Pp. 300, figs. 76. Price 70 Fr.

This is a really good monograph and deals with a subject the importance of which is becoming more widely realized. Arachnoiditis affecting the optic chiasma appears to be either more frequent or more commonly recognized in France than in England, for of the 129 case-records on which this work is based no less than sixty-six are from a single neuro-surgical department, viz. that of Dr. Clovis Vincent at the Hôpital de la Pitié. In every one of these cases the presence of chiasmal arachnoiditis has been verified at operation or post-mortem examination.

Having defined their subject and given a brief historical outline of the recognition of arachnoiditis, the writers demonstrate the normal anatomy of the region of the chiasma and then the abnormalities found in cases of arachnoiditis. The illustrations are numerous, lucid and convincing. Another excellent chapter is that on symptomatology. According to the authors' statistics the commonest syndrome produced is (bi-lateral) central scotoma, this occurring in 31 per cent. of cases. The next most frequent syndrome is simple constriction of the visual fields, and these two groups together make up 54 per cent. of cases. The classical bi-temporal constriction of the fields occurs in only 17 per cent. and other hemianopic syndromes in a further 13 per cent.

The differential diagnosis, forms of treatment, and results, are discussed in the later chapters, and there are analytical tables of all the previously published cases and of the cases personally studied by the writers.

It is evident that the authors are past-masters of their subject, have important matter to present and know well how to present it clearly.

Les Méningo-Neurobrucelloses. Par H. Roger and Y. Poursines. Paris: Masson et Cie. 1938. Pp. 248. Price 45 Fr.

In this valuable monograph the authors bring to notice the fact, hitherto scarcely appreciated by those interested in the Brucella infections, and virtually unknown to neurologists, that these infections are characteristically neurotropic and give rise to a wide range of clinical disorders of nervous function, and this not rarely, but commonly.

They open their account with a general statement of the ætiology and clinical features of Brucella infection, and follow this by a detailed description of the clinical pictures of central and peripheral nervous disorder due to invasion of the nervous system by the responsible organism. The reaction of the meninges, as indicated by examination of the cerebrospinal fluid, is described, but unfortunately there is no account of the morbid anatomy of the nervous system.

The clinical descriptions indicate that nervous involvement occurs late in the course of the infection, and that all parts of the nervous system, meninges, brain, spinal cord and peripheral nerves may be affected.

The studies recorded in this excellent monograph form a notable addition to clinical neurology, and one with which the neurologist should be familiar.

Textbook of Neuro-radiology. By C. P. G. WAKELEY and A. ORLEY. London: Baillière, Tindall and Cox. 1938. Pp. xiv and 336, figs. 229. Price 25s.

The increasingly valuable role of radiography and its various applications in neurological diagnosis make a textbook devoted to this subject a welcome addition to neurological literature. It is probable, however, that the chief value of the present work will be that of a technical guide to neurological radiography for the practising radiologist. The various methods and devices in use for the demonstration of the many pathological changes in the skull and its contents, and in the vertebral column, that are capable of being seen in a radiogram, are described in detail.

Brief clinical descriptions are given of most of these lesions, but these are of doubtful value because they are too short, and do not always emphasize—or even mention—the clinically salient features. Thus, meningioma of the ethmoidal groove is dismissed by the bald statement that its chief diagnostic feature is anosmia—a plainly inadequate summary.

The occurrence of such misspellings as "exopthalmus," "gliomasis" and "subternorial," indicate that greater care in proof reading would have been advantageous. The illustrations are good, but the different sections are unequally supplied in this respect and many of the reproductions of radiograms too small to show adequately the features they are intended to display.

Diabetes Insipidus. By C. FISHER, W. R. INGRAM and S. W. RANSON. Ann Arbor, Michigan: Edward Bros. Inc. 1938. Pp. 196. Price 5 dollars.

This volume embodies the details and results of a series of investigations on the structure and functions of the hypothalamico-hypophyseal system. A salient feature in the experimental method has been the production of lesions in the hypothalamic region by the Clarke-Horsley stereotaxic instrument. There is a detailed clinical study of diabetes insipidus in the cat, and an account of the normal anatomy of the hypothalamus and hypophysis in this animal. Finally, there is a long critical discussion of the relative merits of the hypothalamic and hypophyseal hypotheses concerning the origin of diabetes insipidus.

The authors conclude on the basis of their own observations that: the neural division of the hypophysis controls the flow of water through the kidney, and in respect of this function it fulfils the postulates of an endocrine gland, and on the following grounds: (1) Because its extirpation or atrophy secondary to interruption of the supra-optico-hypophyseal tracts leads to a deficiency symptom, namely,

diabetes insipidus. (2) Because a potent antidiuretic principle can be extracted from it which, injected in minute amount into the blood-stream, produces a marked effect. (3) Because the neural division appears to elaborate this hormone. (4) Because the deficiency symptom can be alleviated by substitution therapy, i.e. the administration of extracts of the neural division containing this antidiuretic hormone.

This book is photolithographed from typescript, the object being to permit of the inexpensive production of scientific works that necessarily command a limited circulation.

Psychotherapy. By PAUL SCHILDER. London: Kegan Paul, Trench, Trübner and Co. 1938. Pp. 344. Price 15s.

The author's expressed purpose is to provide the student, the general physician and the psychiatrist with a knowledge of the technical procedure and the scientific principles upon which to base an approach to psychotherapy. It may be questioned, however, whether with no further knowledge than can be gleaned from so concise a summary of so vast and complex a subject, or without prior experience, the circle of readers named could hope to become successful psychotherapists. Possibly the technique of a physical or of a biological science can be usefully imparted in this simple way, but the thesis that psychotherapy is wholly based upon scientific principles and has no element of art in it is a mode of "wish-fulfilment" that not all will achieve so easily as the author appears to have done. That there is both an art and a science of medicine is an admission that no medical man finds it difficult to make, and psychotherapy will begin to approach the scientific more nearly when its exponents find it possible to make a similar admission. That he should find it impossible to do so indicates that for the psychotherapist, as for the rest of his professional brethren, the command "physician, heal thyself," is still a counsel of perfection.

The various questionnaires given for the benefit of the psychotherapist suggest strongly that the approach to the patient must take account of what the author calls his "ideologies," for they are manifestly not suited for general use, and if so used would bring many budding psychotherapeutic essays to an abrupt conclusion. There is to-day a vast amount of literature and discussion devoted to the study of the *homo sexualis* of Freud and the *homo economicus* of Marx, and the psychotherapist seems so deeply preoccupied with the former of these abstractions that he has overlooked the actual existence of *homo sapiens*. For this Cinderella of the psychologist's cosmos we see small hope of relief—should he ever need this particular form thereof—from a psychotherapy that takes such small account of so many and so important elements in his aspirations.

A Source Book of Gestalt Psychology. By W. D. ELLIS. London: Kegan Paul, Trench, Trübner and Co. 1938. Pp. 403. Price 21s.

The author has translated and reprinted summaries of thirty-four articles which have appeared in Germany during the fifteen years following 1915. Part I contains a statement of the general framework of Gestalt psychology, and Part II gives experimental and clinical details. There is a final section dealing with the various criticisms that have been made by opponents of this school of psychology.

The book is a valuable source of information for all who wish to keep abreast of modern thought in psychology.

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